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COMMUNICATIONS

Published on Web 03/13/2007

Readily Accessible, Modular, and Tuneable BINOL 3,3′-Perfluoroalkylsulfones: Highly Efficient Catalysts for Enantioselective In-Mediated Imine Allylation

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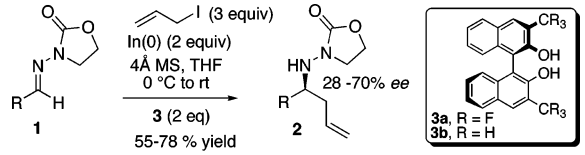
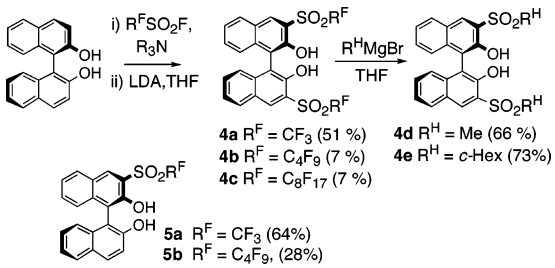
The development of methodologies for the enantioselective allylation of imines[1] is an area that has received much attention.[2] The Si-mediated allylation of *N*-acylhydrazones has been especially successful in this regard. For example, Leighton's modified allylsilane reagents[3] and Kobayashi's sulfoxide/allyltrichlorosilane combination[4] both provide good selectivity (up to 93% ee). Allylindium reagents[5] in combination with chiral auxiliaries such as sulfinimine derivatives,[6] amino acid-derived imines,[7] and α-keto chiral sultams[8] are also effective, and in a prior contribution to this area, we reported[9] that *N*-acylhydrazones bearing an oxazolidinone auxiliary undergo In-mediated allylation with complete diastereocontrol.[10] We subsequently developed an enantioselectively catalyzed allylation of *N*-acylhydrazones (**1** → **2**, Scheme 1). An optimized BINOL derivative (**3a**) was found to induce 70−92% ee,[11,12] and recently Jacobsen reported a urea-based catalyst giving the highest selectivity to date in an analogous process (76−95% ee, R = Ar; 80% ee, R = *i*Pr).[13] Herein we report on modular and tuneable sulfone BINOLs (**4** and **5**) as readily accessible new ligands that prove outstanding in In-mediated allylation, *giving **2** in up to 99% yield and 99% ee*.

One key observation in our prior studies[11] was that the electronic, not steric, demands of the BINOLs **3** proved crucial in determining both the activity and selectivity. For example, the methyl derivative **3b** gave **2a** in 28% ee, inferior to the parent BINOL (→ 45% ee), itself less effective than the optimized 3,3′-bistrifluoromethyl system **3a** (→ 70% ee).[11] Although we have been unable, so far, to isolate the catalyst, NMR evidence (see Supporting Information) suggests that **3a** does not interact directly with the hydrazones (unlike the H-bonding urea catalysts of Jacobsen)[13] but does react with the in situ generated allylindium.[14] The latter process is associated with an upfield shift of the aromatic ^{1}H signals, consistent with BINOL deprotonation by the relatively nonbasic allylindium reagent. As the allylation reaction **1** → (±)-**2** proceeds in the absence of BINOLs (R = Ph, 100% conversion in 11.5 h at room temp) improving catalyst activity is a prerequisite to higher enantioselectivity. On this basis, we sought more Brønsted acidic BINOLs leading to increased Lewis-acidicity in the indium BINOLates. Sulfones in general,[15] and perfluroalkylsulfones (SO_2R^F) in particular, are significantly more electron withdrawing aromatic substituents than CF_3. Indeed, the Hammett σ_p value for SO_2CF_3 ('triflone') is 0.96 compared to a value of 0.54 for CF_3.[15] We recently reported an LDA-mediated thia-Fries rearrangement route to ortho phenolic triflones,[16a] subsequently made general by Butenschön.[16b] We have now conducted double thia-Fries rearrangements which yield electron-demanding, enantiomerically pure 3,3′-bistriflone (**4a**), -nonaflone (**4b**), and -heptadecaflone (**4c**) systems, *in just two steps from BINOL*, Scheme 2. While the (unoptimised) yields of **4bc** are low, they represent the first examples of the rearrangement[16] of higher perfluoralkylsulfonates.

Scheme 1. Enantioselective Allylation Using BINOLs (**3**)[11]



Scheme 2. Rearrangement Route to New Sulfone Ligands



The sulfone BINOL ligand set is readily tuned. For example, mono-rearrangement affords SO_2R^F ligands (**5ab**), and the reaction of *unprotected* **4a** with excess R^HMgBr[17] yields alkylsulfones **4d** and **4e**.[18] These new 3- and 3,3′-sulfone BINOLs were evaluated at 10 mol % loading in the allylation of hydrazones **1ab**. Key results are shown in Table 1, where a stark contrast emerges between **3a** (entries 1 and 2) and the new SO_2R^F catalysts **4a**−**c** (entries 3−6).

As with **3ab**, use of THF as solvent, with 4 Å MS to scavenge water, is essential for selectivity.[11] However, the greater activity of catalysts **4a**−**c** was sufficient to facilitate a switch to an allyl bromide-derived indium reagent, affording even higher selectivity (compare entries 3 and 4). The presence of two SO_2R^F substituents was found to be crucial. The SO_2R^H catalysts **4d** and **4e** gave markedly lower selectivity, particularly for **2b** (entries 7 and 8) and intriguingly, the unsymmetrical catalyst **5a** afforded only 9−11% ee (entry 9). Bromo substituents in the 6,6′ positions of **4a** and **5a** (from 6,6′-Br_2-BINOL) did not significantly alter the results. The remarkable efficacy of bis-SO_2R^F BINOL **4a** was also manifest in a more extensive study, Table 2.

Hydrazones possessing an ortho substituent gave particularly good results (96−99% ee, entries 6−15), facilitating lower catalyst loadings. Indeed, just 3 mol % of catalyst **4a** (entry 9) still gave **2f** in 98% ee. Aliphatic substrates are commonly problematic for the asymmetric allylation reaction, possibly because of their greater reactivity. However, **4a** again afforded significantly improved enantioselectivity (entry 17, 74% ee) as compared to the first generation catalyst **3a** (34% ee).[11] This represents the best example to date of catalytic enantioselective indium-mediated allylation of a linear[13] aliphatic substrate.

In conclusion, we report modular and tuneable new enantiomerically pure sulfones, accessible in just two steps from BINOL.

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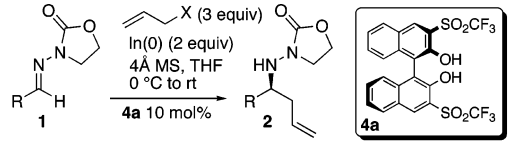
10.1021/ja070742t CCC: $37.00

Table 1. Comparison of BINOL **3a** with Sulfones **4/5** (10 mol %)[a]

		2a (R = Ph)		**2b** (R = styryl)	
entry	BINOL (10 mol %)	yield %	ee %[b]	yield %	ee %[b]
1	**3a**	77	70	79	34
2	**3a** (200 mol %)	78	70		
3	**4a**	95	88	85	90
4[c,d,e]	**4a**	**82**	**90**	**87**	**97**
5[c]	**4b**	68[c]	89[c]		
6[c]	**4c**	72[c]	88[c]		
7	**4d**	49	49	71	44
8	**4e**	98	68	87	10
9	**5a**	59	11	70	9

[a] Conditions as Scheme 1. [b] Chiral HPLC. [c] Using allyl bromide. [d] 100% conversion, 4 h, 0−4 °C. Same conditions, with 0 mol % **4a**, 23% (±)-**2a**. [e] No reaction in DMF, CH_2Cl_2, or MeCN. In 75% aq THF **2a** obtained in 20% yield, 33% ee

Table 2. Enantioselective Allylation Catalyzed by **4a** (10 mol %)[a]



			X = I		X = Br	
entry	hydrazone		yield %[b]	ee %[c]	yield %[b]	ee %[c]
1	**a**		95	88	82	**90**
2	**b**		85	**90**	87	**97**
3	**c**	Me	95	87	98	87
4	**d**	MeO	88	**95**	96	**95**
5	**e**	Cl	98	**90**	96	**92**
6	**f**	Br	98	**97**	96	**99**
7			(**4a** 5 mol%)		99	**99**
8			(**4a** 4 mol%)		96	**98**
9			(**4a** 3 mol%)		94	**98**
10			(**4a** 2 mol%)		94	**95**
11			(**4a** 1 mol%)		95	88
12	**g**	Cl	95	**97**	99	**99**
13	**h**	Me	84	**97**	98	**99**
14	**i**	OMe	97	**94**	98	**96**
15	**j**		95	**96**	96	**98**
16	**k**	O	97	**90**	94	**92**
17	**l**		93	74	88	70

[a] The allylindium/ligand complex was preformed. See Supporting Information for details. [b] Yield and ee are the average of at least two runs. [c] Chiral HPLC.

The bis-SO_2R^F BINOL **4a** facilitates a general and highly enantioselective catalytic indium-mediated imine allylation, affording **2** in up to 99% ee. This represents the highest selectivity to date in any indium-mediated allylation and the catalyst is easily recovered (silica-gel chromatography) and recycled (×3) without loss of activity or selectivity. The SO_2R^F BINOL systems (**4a**−**c**) offer significant opportunities for exploiting fluorous phase technologies[19] in this and other reactions.

Acknowledgment. We are grateful to the National Science Foundation (Grant NSF-CHM-0616485) and the European Union (STRP 505167-1 LIGBANK) for financial support. We thank Pfizer and ND-EPSCoR for graduate fellowships (R.K.).

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA070742T