ORGANIC LETTERS

2004
Vol. 6, No. 16
2701−2704

Asymmetric Allylboration of Aldehydes and Ketones Using 3,3′-Disubstitutedbinaphthol-Modified Boronates

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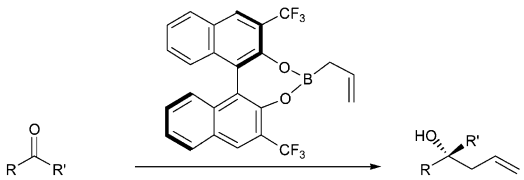
Received May 18, 2004

ABSTRACT



Allylboronates derived from 3,3′-disubstituted 2,2′-binaphthols react with aldehydes and ketones to give the expected allylated products with up to >99:1 er. Highest selectivities were observed for aromatic ketones. The bis(trifluoromethyl) derivative is particularly outstanding in terms of reactivity, selectivity, and robustness.

1,1′-Bi-2-naphthol (BINOL, **1**) has been used extensively in asymmetric synthesis for the past 2 decades.[1] Since the seminal work reported by Noyori in 1981 on asymmetric reductions using BINOL-modified aluminum hydrides,[2] this ligand has been used very successfully for a wide variety of asymmetric processes.[3]

Derivatives of BINOL, particularly 3,3′-disubstituted derivatives, have also been used in asymmetric synthesis.[4] The pioneering contributions of Kelly[5] and Yamamoto[6] showed that dramatic increases in enantioselectivities could be achieved with 3,3′-disubstituted BINOLs compared to BINOL itself. More recently 3,3′-disubstituted BINOLs have been used to obtain increased enantioselectivities in 1,2-additions of dialkylzincs to aldehydes,[7] conjugate additions of diethylzinc to enones,[8] aldol reactions,[9] cyanosilylations,[10] olefin metathesis reactions,[11] and hetero-Diels−Alder reactions.[12] There is also a report that substitution at the 3,3′-positions of BINOL gave decreased enantioselectivities in hydrophosphonylation of aldehydes.[13]

We have previously shown that 3,3′-disubstitution can have a dramatic effect on the asymmetric conjugate alkynylations of enones using alkynylboronates.[14] Thus, with

(1) See, for example: (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995. (b) Pu, L. *Chem. Rev.* **1998**, *98*, 2405−2494.

(2) Nishizawa, M.; Yamada, M.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 247−250.

(3) Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336−10348 and references therein.

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(5) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510−3512.

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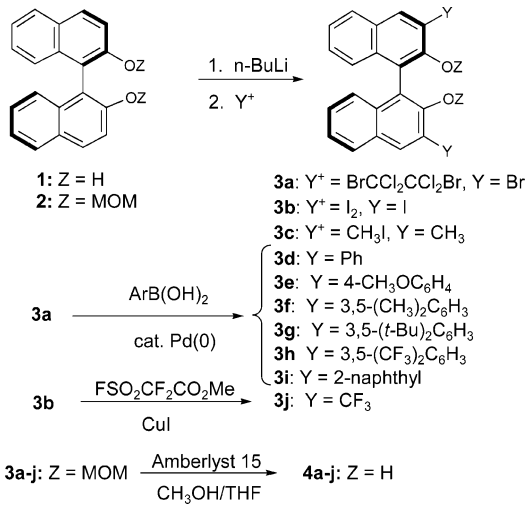
(12) (a) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10−11. (b) Du, H.; Long, J.; Hu, J.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 4349−4352. (c) Du, H.; Ding, K. *Org. Lett.* **2003**, *5*, 1091−1093.

10.1021/ol0490882 CCC: $27.50
Published on Web 07/16/2004

BINOL as ligand, selectivities were never better than ~60:40 er, whereas reagents prepared with 3,3′-Ph_2BINOL gave selectivities up to >99:1 er. We now report that 3,3′-Ph_2-BINOL and other 3,3′-disubstituted binaphthols can also be used to prepare other boronates that can be used in reactions such as allylborations with excellent results.

3,3′-Disubstituted BINOLs could be easily prepared from MOM derivative **2** (Scheme 1).[15] Thus lithiation of **2** followed by trapping with the appropriate electrophiles gave **3a**−**c**. Dibromide **3a** underwent Suzuki cross-coupling with arylboronic acids to afford the expected diaryl derivatives **3d**−**i**. The trifluoromethyl derivative **3j** proved to be problematic but was eventually obtained by treating iodide **3b** with methyl fluorosulfonyldifluoroacetate and CuI.[16] Finally, each of the MOM derivatives could be deprotected using Amberlyst 15 in THF/MeOH to give the desired substituted BINOLs **4** in excellent yields.

Scheme 1

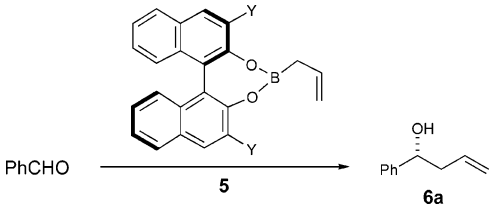


Ligand **4j**, bearing trifluoromethyl groups at the 3,3′-positions,[17] was of particular interest. The intent was that the strongly electron-withdrawing CF_3 groups should make any derived boronates more electrophilic and hence more reactive toward carbonyl compounds. The CF_3 groups should also be sufficiently large such that good selectivities should be possible.

An intriguing application of ligands **4** is the allylboration of carbonyl compounds. Asymmetric allylborations have become very important in synthesis.[18] Other chiral diols have been used to prepare allylboronates that can effect allylation of aldehydes with variable selectivities.[19] Tartrate derivatives, developed extensively by Roush and used in many natural product syntheses, are the most popular diols.[20] There is one report of an allylboronate derived from BINOL being used for allylations, but benzaldehyde was the only substrate examined.[21] Thus it seemed worthwhile to investigate this reaction further and particularly to examine the effect of the 3,3′-substituent.

Allylboronates **5** could be easily prepared by treating binaphthols **4** with triallylborane.[22] In general, the resulting reagents reacted rapidly with PhCHO in THF[23] at −78 °C to afford the expected homoallylic alcohol in high yield (Table 1).

Table 1. Reactions of Allylboronates **5** with PhCHO[a]



entry	reagent[a] Y	reagent[a] compd no.	yield of **6a**[b] (%)	er of **6a**[c] (*R*:*S*)
1	H	**5a**	50	71:29
2	I	**5b**	91	87:13
3	CH_3	**5c**	91	88:12
4	Ph	**5d**	90	73:27
5	4-$CH_3OC_6H_4$	**5e**	89	81:19
6	3,5-$(CH_3)_2C_6H_3$	**5f**	94	80:20
7	3,5-(*t*-Bu)$_2C_6H_3$	**5g**	92	83:17
8	3,5-$(CF_3)_2C_6H_3$	**5h**	92	85:15
9	2-naphthyl	**5i**	90	75:25
10	CF_3	**5j**	90	98:2

[a] Reactions were run in THF at −78 °C, 1 h. [b] Isolated yields of chromatographed products. [c] Determined by HPLC analysis with a Chiralcel OD column.

Somewhat surprisingly, the allylboronate derived from BINOL (**1**) and 3,3′-Ph_2-BINOL (**4d**) gave comparable selectivities, and these were the lowest selectivities observed (entries 1 and 4). We were unable to reproduce the 94:6 selectivity previously reported for allylation of PhCHO using reagent **5a** (prepared from **1**).[21] Other aryl-substituted binaphthols (entries 5−9) gave slightly higher but unspectacu-

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(14) Chong, J. M.; Shen, L.; Taylor, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 1822−1823.
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(17) When this work was conceived, binaphthol **4j** was an unknown compound. It has since appeared in the Japanese patent literature: JP 2002356454 as quoted in CAN 138:39104 and JP 2001139508 as quoted in CAN 134:366697. It was used to make a chiral Zr catalyst for hetero-Diels−Alder reactions.
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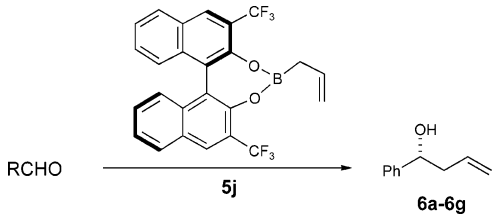
(22) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186−8190.
(23) Other solvents surveyed ($PhCH_3$, CH_2Cl_2, CH_3CN, ether) using reagent **5j** and PhCHO gave respectable (91:9−95:5) but lower enantioselectivities.

lar selectivities. The iodo and methyl analogues (entries 2 and 3) showed small improvements in selectivity.

Much to our delight, reagent **5j**, derived from 3,3′-$(CF_3)_2$-BINOL (**4j**), gave by far the best selectivity (Table 1, entry 10). It also showed the highest reactivity, with allylation of PhCHO complete within 5 min at −78 °C. Allylation of other aldehydes using **5j** proceeded smoothly at −78 °C to give products in high yields (Table 2). High selectivities were

Table 2. Allylation of Aldehydes with Boronate **5j**[a]



		6		
entry	aldehyde R	compd no.	yield[b] (%)	er[c] (*R*:*S*)
1	Ph	**6a**	90	98:2
2	4-$CH_3OC_6H_4$	**6b**	93	97:3
3	4-ClC_6H_4	**6c**	93	97:3
4	4-$O_2NC_6H_4$	**6d**	96	96:4
5	4-$CF_3C_6H_4$	**6e**	94	97:3
6	PhCH=CH	**6f**	98	88:12
7	*c*-C_6H_{11}	**6g**	90	88:12

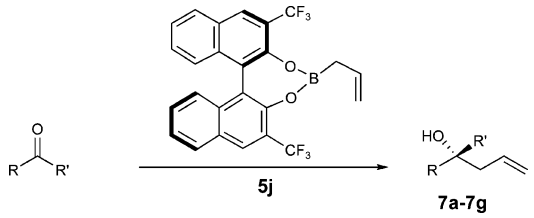
[a] Reactions were run in THF at −78 °C, 1 h. [b] Isolated yields of chromatographed products. [c] Determined by HPLC analysis with a Chiralcel OD column.

observed for all of the aromatic aldehydes examined (Table 2, entries 1−5). High yields but slightly lower selectivities were found with an enal (cinnamaldehyde) and an aliphatic aldehyde (Table 2, entries 6 and 7).

Allylboronate **5j** also reacted with ketones, albeit much more slowly than with aldehydes (Table 3). Thus, whereas aldehydes usually showed complete reaction with **5j** within 5 min at −78 °C, acetophenone was only partially consumed and the expected 3° alcohol 7**a** was isolated in a modest 60% yield even after 6 h at −78 °C. However, the enantioselectivity observed (er = 98:2) was excellent (Table 3, entry 1). The yield of **7a** could be improved by allowing the reaction to warm to −40 °C with only a small drop in enantioselectivity (entry 2). Other alkyl aryl ketones were allylated with uniformly high selectivities (entries 3−5). An α,β-unsaturated ketone, benzalacetone, gave lower but still respectable selectivity. Pinacolone (*t*-Bu vs Me) was also allylated with good selectivity (entry 7), but poor enantiofacial discrimination was observed for a ketone with sterically similar alkyl groups (entry 8). In all cases, reactions were very clean with near quantitative conversion to the desired 3° alcohol. High isolated yields were typically observed with the lower yield of **7f** attributable to its volatility.

Asymmetric allylboration of ketones is typically a very poor reaction. For example, allylboration of acetophenone with $Ipc_2BCH_2CH{=}CH_2$ gives **7a** with 5% ee.[24] There appear

Table 3. Allylation of Ketones with Boronate **5j**[a]



	ketone		7		
entry	R	R′	compd no.	yield[b] (%)	er[c] (*R*:*S*)
1	Ph	CH_3	**7a**	60[d]	98:2
2	Ph	CH_3	**7a**	88	96:4
3	Ph	CH_2Br	**7b**	87[e]	97:3
4	4-$CH_3OC_6H_4$	CH_3	**7c**	95	99:1
5	4-ClC_6H_4	CH_3	**7d**	94	>99:1[f]
6	PhCH=CH	CH_3	**7e**	91	88:12
7	*t*-Bu	CH_3	**7f**	75	95:5[g]
8	$PhCH_2CH_2$	CH_3	**7g**	98	75:25

[a] Reactions were run in toluene at −78 to −40 °C, 48 h. [b] Isolated yields of chromatographed products. [c] Determined by HPLC analysis with a Chiralcel OD column. [d] Reaction was run in toluene at −78 °C, 6 h. [e] Isolated yield of 1-phenyl-1-(2-propenyl)oxirane after workup with 1 M NaOH. [f] The minor enantiomer was not detected by HPLC analysis. [g] Determined by ^1H NMR analysis in the presence of $Eu(hfc)_3$.

to be no previous reports of enantioselective allylborations of ketones using allylboronates. This is likely due to the low reactivity of most allylboronates toward ketones or to low selectivities observed that were therefore not reported. Ketones bearing adjacent coordinating groups show higher reactivities toward allylboronates, and diastereoselective reactions have been reported.[25] In the case of **5j**, higher reactivity is undoubtedly due to the electron-withdrawing CF_3 groups.[26] Roush has previously shown that addition of fluorinated groups to a tartramide leads to higher reactivity (in aldehyde allylations) in the derived allylboronate.[20]

The high selectivities obtained with **5j** compare very favorably with other methods for the asymmetric allylation of ketones.[27] In fact, boronate **5j** is one of the most selective reagents for the allylation of alkyl aryl ketones thus far developed. The yields and selectivities observed with substituted acetophenones (Table 3, entries 4 and 5) are particularly impressive.

The absolute configurations of the major products in the allylation of both aldehydes and ketones were determined by comparison of optical rotations with known materials.[28]

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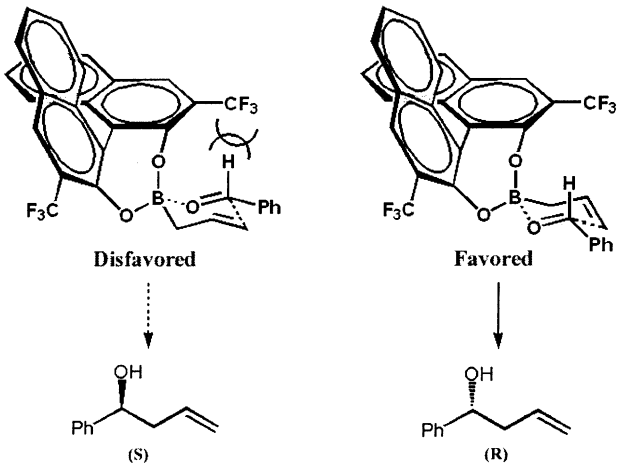
(28) See Supporting Information for details.

In each case, allylations using *R*-BINOLs all gave *R* alcohols as major products. The sense of asymmetric induction using allylboronates **5j** may be explained using a six-membered chair transition-state model (Scheme 2). In this model, the

Scheme 2



larger or aryl group occupies an equatorial position in either of two possible transition states. The 3- and 3′-substituents on the binaphthol play an important role in destabilizing one of the possible transition states. In the case of aldehydes, this destabilizing interaction is between a CF_3 group and the aldehydic H, whereas with ketones it would be between a CF_3 group and the smaller group of the ketone, usually a methyl group.

It should be noted that although stoichiometric amounts of ligand **4j** are used in these reactions (as opposed to the metal-catalyzed allylborations recently developed[29,30]), the binaphthol is easily recovered from the reaction in near-quantitative yields and with no detectable racemization by simple extraction with aqueous base. In fact, **4j** seems to be extremely resistant to racemization. Even under strongly acidic conditions (10% HCl, H_2O−THF, reflux, 24 h) or basic (0.1 M KOH, *n*-BuOH, 60 °C, 48 h) that cause complete racemization of BINOL, **4j** shows no detectable racemization. This remarkable configurational stability is likely due, at least in part, to the strongly electron-withdrawing character of the CF_3 group. Yudin introduced an octafluoro-BINOL that showed much higher configurational stability compared to that of BINOL.[31] Although this increased stability is very desirable, synthetic challenges in preparing enantiomerically pure F_8-BINOL have limited its applications. In contrast, 3,3′-$(CF_3)_2$-BINOL **4j** is easily prepared from BINOL **1**, which is commercially available in either enantiomeric form, in four steps with 80% overall yield.

In summary, we have shown that 3,3′-disubstituted-BINOLs can be used to prepare allylboronates that will allylate carbonyl compounds. 3,3′-$(CF_3)_2$-BINOL **4j** is an especially effective auxiliary that allows for allylborations of both aldehydes and ketones in high enantioselectivities. We anticipate that many other applications of **4j** in asymmetric synthesis will be found.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support, and Mr. D. Gehle for racemization studies on binaphthol **4j**.

Supporting Information Available: Experimental details for the preparation of and spectral data for compounds **2**−**4**, procedures for allylations, and details for determinations of enantiomer ratios and absolute configurations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0490882

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