ORGANIC LETTERS

2013
Vol. 15, No. 7
1710–1713

Asymmetric Methallylation of Ketones Catalyzed by a Highly Active Organocatalyst 3,3′-F_2-BINOL

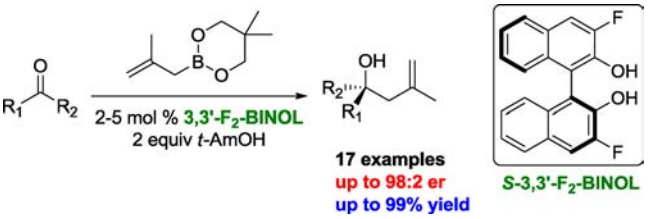
Yongda Zhang,* Ning Li, Bo Qu, Shengli Ma, Heewon Lee, Nina C. Gonnella, Joe Gao, Wenjie Li, Zhulin Tan, Jonathan T. Reeves, Jun Wang, Jon C. Lorenz, Guisheng Li, Diana C. Reeves, Ajith Premasiri, Nelu Grinberg, Nizar Haddad, Bruce Z. Lu, Jinhua J. Song, and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road/P.O. Box 368, Ridgefield, Connecticut 06877-0368, United States

yongda.zhang@boehringer-ingelheim.com

Received February 22, 2013

ABSTRACT



(*S*)-3,3′-F_2-BINOL has been synthesized for the first time and demonstrated as a highly active organocatalyst for asymmetric methallylation of ketones. Up to 98:2 enantioselectivity and 99% yield were obtained with 5 mol % catalyst loading. The catalyst (*S*)-3,3′-F_2-BINOL could be easily recovered and reused.

Chiral tertiary alcohols are commonly found motifs in biologically active compounds. Recently, we needed to develop a practical process for constructing a key chiral building block **1** (Scheme 1) for a pharmaceutical agent. The most direct synthetic strategy to install the chiral tertiary alcohol subunit would involve an asymmetric *methallylation* of ketone **3**. A literature survey revealed that although much effort has been dedicated to the area of asymmetric allylation of ketones,[1] there is a lack of efficient, practical, and environmentally benign methods for the corresponding asymmetric methallylation of ketones.[2] The first catalytic asymmetric methallylation of ketones with tetramethylallylstannane was reported by Walsh and co-workers in 2006.[2a] Shortly after, a chromium-catalyzed enantioselective addition of allyl bromide to ketones was described by the Sigman group[2c] and only one example was reported for asymmetric methallylation. In both cases, toxic metals such as tin and chromium were employed in the transformation. Moreover, the optimized and well-developed conditions for allylation of ketones were not always directly applicable to the methallylation process due to the unclear and elusive mechanistic differences between the two processes.[2a] Given the importance of the asymmetric methallylation reaction of ketones, it was highly desirable to develop new catalytic conditions for this transformation. Our efforts in this area focused on organocatalysis considering its mild conditions, operational simplicity, and environmental benefits. Herein we would like to report a highly practical and efficient process for asymmetric methallylation of ketones using 3,3′-F_2-BINOL as the organocatalyst.

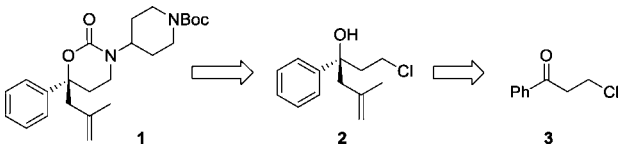
Recent literature has suggested that Brønsted acids are capable of activating allylboronates for nucleophilic addition reactions to carbonyl compounds.[3] In particular, Schaus et al. described an asymmetric allylboration of ketones catalyzed by 3,3′-Br_2-BINOL.[4] Intrigued by their work, we prepared the corresponding methallyl boronate **4** and applied these allylation conditions to the

(1) For asymmetric allylation of ketones, see reviews: (a) Hatano, M.; Ishihara, K. *Synthesis* **2008**, *11*, 1647. (b) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. (c) Tietze, L. F.; Kinzel, T.; Brazel, C. C. *Acc. Chem. Res.* **2009**, *42*, 367.

(2) (a) Kim, J. G.; Camp, E. H.; Walsh, P. J. *Org. Lett.* **2006**, *8*, 4413. (b) Román, J. G.; Soderquist, J. A. *J. Org. Chem.* **2007**, *72*, 9772. (c) Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752. (d) Hanhan, N. V.; Tang, Y. C.; Tran, N. T.; Franz, A. K. *Org. Lett.* **2012**, *14*, 2218.

10.1021/ol400498a
Published on Web 03/25/2013

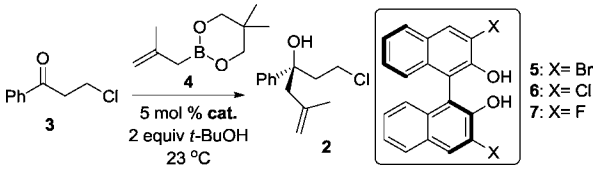
Scheme 1



methallylation reaction using our substrate **3** (Table 1). Our initial studies showed that the use of 3,3′-Br_2-BINOL **5** for the *methallylation* of ketone **3** with cyclic boronate **4** gave reasonable enantioselectivities. However, the reaction proved to be sluggish, giving poor conversions (61% after 10 h with 5 mol % catalyst **5**, entry 1). The observed low catalytic activity of 3,3′-Br_2-BINOL for methallylation prompted us to further investigate this reaction, aiming at identifying a more reactive catalyst for the asymmetric methallylation of ketones.

Our approach is based on the hypothesis that catalytic activities of substituted BINOLs can be modulated by the substituents at the 3,3′-positions of the biaryl skeleton. We envisioned that by increasing the acidity of the substituted BINOLs, we might be able to improve the catalyst reactivity for the challenging ketone methallylation. To test this hypothesis, we prepared a range of chiral BINOL derivatives with electron-withdrawing groups and tested them in the asymmetric methallylation of ketone **3** (Table 1).[5] Our results indicated that the use of chiral BINOLs containing CF_3,[6] CO_2Me, or SO_2CF_3[7] at the 3,3′-positions gave essentially no enantioselectivity (entries 2−4). Yet, when we introduced Cl substituents at the 3,3′-positions of BINOL,[8] the methallylation with ketone **3** proved to be faster than the reaction with 3,3′-Br_2-BINOL **5**, giving 70% conversion and good enantioselectivity (91:9 er, entry 5). Encouraged by these results, we decided to install an even more electron-withdrawing halogen, i.e. fluorine, at the 3,3′-positions of BINOL. After an extensive literature search, we were surprised to find that, despite decades of

Table 1. Asymmetric Methallylation of Ketone **3**

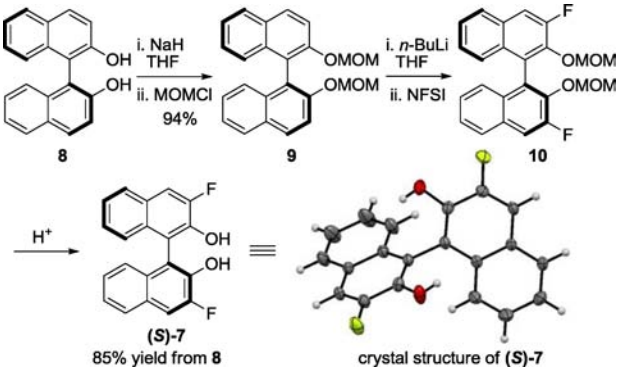


entry[a]	X	t (h)	conv (%)	er[b]
1	Br	10	61	89:11
2	CO_2Me	16	84	51:49
3	SO_2CF_3	20	88	50:50
4	CF_3	16	82	52:48
5	Cl	10	70	91:9
6	**F**	**10**	**98**	**87:13**

[a] All reactions were performed with ketone **3** (1.0 equiv) and boronate **4** (1.2 equiv) under nitrogen. [b] The er was determined by chiral HPLC of the reaction mixture.

extensive research on BINOL derivatives,[9] 3,3′-F_2-BINOL **7** has never been synthesized before, presumably due to the difficulties associated with its synthesis. To examine its catalytic activity, we first developed an efficient synthetic route to 3,3′-F_2-BINOL **7** as shown in Scheme 2. Directed-ortho-metalation of compound **9** generated the lithium dianion, which was trapped with NFSI (*N*-fluorobenzenesulfonimide) to give intermediate **10**.[10] Subsequent acidic deprotection furnished the desired product **7** in 85% overall yield from BINOL **8**. The structure of **7** was confirmed by NMR as well as the single crystal X-ray analysis. Multikilograms of 3,3′-F_2-BINOL were readily prepared using this procedure.

Scheme 2



To our delight, the methallylation reaction with 3,3′-F_2-BINOL **7** as the catalyst proved to be much more facile

(3) (a) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. (b) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426. (c) Nowrouzi, F.; Thadani, A. N.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2631. (d) Matsuoka, H.; Kondo, K. *Tetradedron Lett.* **2009**, *50*, 2320. (e) Meilly, M. K.; Ryschnovsky, S. D. *Org. Lett.* **2010**, *12*, 4895.

(4) (a) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (b) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8679.

(5) See Supporting Information for a full list of screening results of various substituted BINOLs.

(6) Cook, G. R.; Kargbo, R.; Maity, B. *Org. Lett.* **2005**, *7*, 2767.

(7) Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G. R.; LIoyd-Jones, G. C.; Shepperson, I. R. *J. Am. Chem. Soc.* **2007**, *129*, 3846.

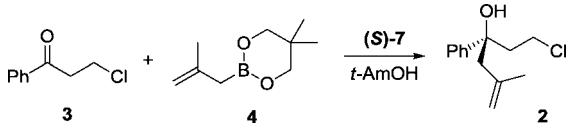
(8) Examples of application 3,3′-Cl_2-BINOL: (a) Orito, Y.; Hashimoto, S.; Ishizuka, T.; Nakajima, M. *Tetrahedron* **2006**, *62*, 390. (b) Turner, H. M.; Patel, J.; Niljianskul, N.; Chong, J. M. *Org. Lett.* **2011**, *13*, 5796. (c) Ichibakase, T.; Kaneko, T.; Orito, Y.; Kotani, S.; Nakajima, M. *Tetrahedron* **2012**, *68*, 4210. (d) Ito, K.; Takahashi, M.; Hoshino, T.; Nishiki, M.; Ohba, Y. *Letters in Org. Chem.* **2006**, *3*, 735. (e) Ichibakase, T.; Orito, Y.; Nakajima, M. *Tetrahedron Lett.* **2008**, *49*, 4427.

(9) (a) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269. (b) Brunel, J. M. *Chem. Rev.* **2007**, *107*, PR1–PR45. (c) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (d) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155. (e) Pu, L. *Chem. Rev.* **1998**, *98*, 2405. (f) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

(10) (a) Snieckus, V.; Beaulieu, F.; Morhri, K.; Han, W.; Murphy, C. K.; Davis, F. A. *Tetrahedron Lett.* **1994**, *35*, 3465. (b) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253. (c) Dofferding, E.; Ofner, H. *Synlett* **1991**, 187.

than reactions with 3,3′-Br_2-BINOL and 3,3′-Cl_2-BINOL. With 5 mol % of **7**, the reaction reached 98% conversion in 10 h with 87:13 er (Table 1, entry 6). To the best of our knowledge, this is the first time that 3,3′-F_2-BINOL has been synthesized and utilized to catalyze organic reactions.

Table 2. Asymmetric Methallylation of Ketone **3** with 3,3′-F_2-BINOL **7** as the Organocatalyst



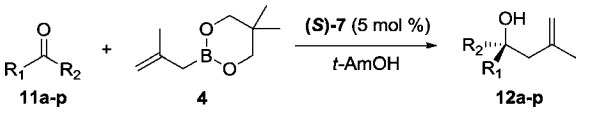
entry[a]	**7** (mol %)	t (°C)	t (h)	er[b]	conv (%)[c]
1	5	23	10	86:14	98[d]
2	5	23	10	86:14	98
3	5	0	41	87:13	73
4	5	40	8	86:14	98
5	5	60	3	85:15	98
6	2	23	41	84:16	98

[a] All reactions were performed with ketone **3** (1.0 equiv), boronate **4** (1.2 equiv), 3,3′-F_2-BINOL **7**, and *t*-AmOH (2 equiv) under nitrogen at the temperature indicated in the table unless noted otherwise. [b] The er was determined by chiral HPLC of the reaction mixture. [c] HPLC conversion of **3** to **2** at 220 nm. [d] *t*-BuOH was used.

Further optimization was focused on defining the reaction temperatures as well as the loading of the catalyst and the alcohol additive. The use of *t*-BuOH or *t*-AmOH gave similar results in the asymmetric methallylation (Table 2, entries 1−2). For convenience, *t*-AmOH was chosen for further studies because of its lower melting point. To improve the enantioselectivities, we attempted to perform the reaction at lower temperatures. Interestingly, our results indicated that the enantioselectivity, unlike the reaction rate, is independent of the reaction temperature. At 0 °C, in the presence of 5 mol % of catalyst **7**, the reaction gave the same enantioselectivity (87:13) (entry 3). On the other hand, the reaction tolerated high temperatures, allowing faster conversion without significant erosion of enantioselectivity.[11] With 5 mol % of **7**, the reaction reached 98% conversion after 3 h at 60 °C or 8 h at 40 °C, still with good enantiomeric ratios (entries 4−5). The catalyst loading can be decreased to 2 mol %, and excellent conversion was still achieved after 41 h at 23 °C while maintaining the similar level of enantioselectivity (entry 6). It should be noted that 3,3′-F_2-BINOL can be easily recycled via base−acid extraction during the workup. Considering the ready availability and recyclability of 3,3′-F_2-BINOL, the catalyst loading is not a critical issue for this process and all the subsequent work was carried out using 5 mol % of **7**.

(11) In the case of 3,3′-Br_2-BINOL **5** and 3,3′-Cl_2-BINOL **6**, the reactions at high temperature led to low conversion.

Table 3. Asymmetric Methallylation of Ketones **11a**−**p** with 3,3′-F_2-BINOL **7** as the Organocatalyst



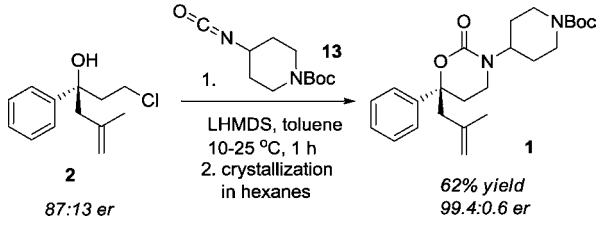
entry[a]	ketone		product	t (h)[b]	T (°C)	yield (%)[c]	er[d]
1	**11a**	R^1 = Ph, R^2 = CH_2Ph	**12a**	4	40	98	93:7[e]
2	**11b**	R^1 = Ph, R^2 = CH_2(3-$MeOC_6H_4$)	**12b**	5	40	95	96:4
3	**11c**	R^1 = 2-$MeOC_6H_4$, R^2 = CH_2Ph	**12c**	18	23	97	95:5
4	**11d**	R^1 = 4-FC_6H_4, R^2 = CH_2Ph	**12d**	2	40	97	96:4
5	**11e**	R^1 = 4-ClC_6H_4, R^2 = CH_2Ph	**12e**	2	40	97	96:4
6	**11f**	R^1 = 4-BrC_6H_4, R^2 = CH_2Ph	**12f**	2	40	98	97:3
7	**11g**	R^1 = 2-$MeOC_6H_4$ R^2 = CH_2(1-naphthyl)	**12g**	18	40	96	93:7
8	**11h**	R^1 = 2-$MeOC_6H_4$ R^2 = CH_2(2-naphthyl)	**12h**	5	40	99	98:2
9	**11i**	R^1 = 4-ClC_6H_4, R^2 = $(CH_2)_2Cl$	**12i**	18	23	95	85:15
10	**11j**	R^1 = 3-thienyl, R^2 = CH_2Ph	**12j**	18	23	98	96:4
11	**11k**	R^1 = 2-thienyl, R^2 = CH_2Ph	**12k**	18	23	97	97:3
12	**11l**	R^1 = Ph,R^2 = $(CH_2)_2Ph$	**12l**	4	40	97	91:9
13	**11m**	R^1 = Ph,R^2 = $(CH_2)_3Ph$	**12m**	4	40	96	90:10
14	**11n**	R^1 = Ph,R^2 = CH_2OBn	**12n**	18	23	93	85:15
15	**11o**	R^1 = Ph,R^2=CH_3	**12o**	18	23	96	78:22
16	**11p**	R^1 = Ph, R^2 = $CH_2CO_2{}^tBu$	**12p**	18	23	95	78:22

[a] All reactions were performed with ketone **11a**−**q** (1.0 equiv), 3,3′-F_2-BINOL **7** (0.05 equiv), boronate **4** (1.5 equiv), and *t*-AmOH (2 equiv) under nitrogen. [b] The reaction time was not optimized. [c] Isolated yields after chromatography purification on silica gel. [d] The er was determined on chiral HPLC. [e] 0.02 equiv of **7** was used.

To delineate the scope of this asymmetric process using 3,3′-F_2-BINOL **7** as the organocatalyst, a variety of ketones **11a**−**q** were methallylated under the standard reaction conditions (5 mol % catalyst **7**, 1.5 equiv of boronate **4**, 2 equiv of *t*-AmOH, Table 3). In the case of 1,2-diphenylethanone **11a**, the reaction went to completion in 4 h at 40 °C to give product **12a** in 98% yield and 93:7 er (Table 3, entry 1). High enantioselectivities were obtained on substrates with an electron-donating substituent on either of the phenyl rings of 1,2-diphenylethanone (entries 2−3). Due to low solubility under the reaction conditions, no reaction was observed at 23 °C overnight for halogenated 1,2-diphenylethanones **11d**, **11e**, and **11f**. Fortunately, the current protocol allowed the reaction to be run at higher temperatures. At 40 °C, reactions with all three ketones were successful and produced the corresponding products **12d**, **12e**, and **12f** in excellent enantioselectivities (entries 4−6). Ketones **11g** and **11h**, containing the naphthyl group at the 2-position of phenylethanone, were examined, and both reactions were performed at 40 °C for completion and generated products **12g** and **12h** with high stereoselectivities (entries 7−8). In comparison with ketone **3**, the reaction with ketone **11i** bearing a fluorine substituent at the para-position of phenyl ring was slower, indicating a negative effect of the electron-withdrawing groups. With 5 mol % of **7**, full conversion of **11i** was achieved at 23 °C in 18 h (entry 9). Excellent results

were also obtained with heteroaromatic ketones such as **11j** and **11k** (entries 10−11). The reaction also worked well for 1,3-diphenylpropan-1-one **11l** and 1,4-diphenylbutan-1-one **11m**, giving products **12l** and **12m** in 91:9 and 90:10 er, respectively (entries 12−13). In the case of 2-(benzyloxy)-1-phenylethanone **11n**, good enantioselectivity (86:14) was observed (entry 14). For acetophenone **11o**, a simple ketone, the reaction gave the product **12o** in moderate enantioselectivity (78:22 er) at 23 °C (Table 3, entry 15). Catalyst **7** could also be applied to β-keto esters such as **11p**, a type of difficult substrates due to the propensity to enolize (entry 16). We were delighted to find that compound **11p** underwent smooth ketone methallylation under standard conditions in excellent yield and with moderate enantioselectivity (78:22 er).

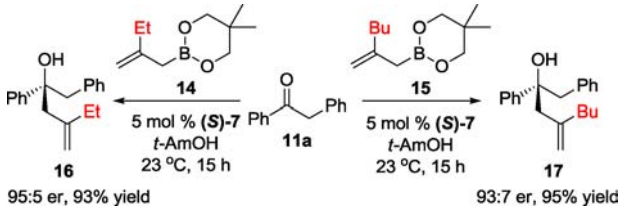
Scheme 3



The newly developed asymmetric methallylation reaction with 3,3′-F_2-BINOL allowed us to access our desired chiral tertiary alcohol synthon **1** for the rapid construction of a variety of pharmaceutically active molecules. The process of asymmetric methallylation of **3** was successfully carried out on kilogram scale to give product **2** in 95% yield with 87:13 er after simple workup. A subsequent reaction of alcohol **2** with isocyanate **13** provided cyclic carbamate product **1** in 62% yield after crystallization. The enantiomeric purity of **1** was readily enriched from 87:13 to 99.4:0.6 during the crystallization process (Scheme 3).

To further demonstrate the synthetic utility of **7** as the organocatalyst for the alkylallylation of ketones, more sterically hindered boronates **14** and **15** were synthesized and evaluated (Scheme 4). To our delight, both **14** and **15** were able to undergo complete reactions with ketone **11a** with 3,3′-F_2-BINOL as the catalyst. With 5 mol % of the catalyst, product **16** derived from **14** was isolated in 93% yield and 95:5 er after 15 h. The reaction with **15** gave **17** with 93:7 er under similar conditions.

Scheme 4



In conclusion, we have synthesized 3,3′-F_2-BINOL for the first time and employed it as a highly active organocatalyst for asymmetric methallylation of ketones with excellent yields and high enantioselectivities. It is noteworthy that 3,3′-F_2-BINOL exhibited significantly higher catalytic activity than 3,3′-Br_2-BINOL and 3,3′-Cl_2-BINOL for the methallylation of ketones. We have also synthesized boronates **14** and **15** which proved to be effective alkylallylating agents. The new asymmetric methallylation method represents an efficient, practical, and green process considering the ready availability and recyclability of 3,3′-F_2-BINOL, as well as the solvent-free and near ambient temperature reaction conditions. The process has been demonstrated on kilogram scales for the preparation of enantiomerically enriched synthon **1**, a valuable building block for medicinal chemistry. It is important to note that rate acceleration by 3,3′-F_2-BINOL actually made this process viable, and we believe in the future that the 3,3′-F_2-BINOL derived catalytic systems can be utilized in tuning the reaction rates in many other asymmetric transformations. Further work using 3,3′-F_2-BINOL as an organocatalyst or a chiral ligand for other catalytic asymmetric C−C bond-forming reactions is ongoing.

Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.