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Asymmetric Synthesis of Propargylamides via 3,3′-Disubstituted Binaphthol-Modified Alkynylboronates

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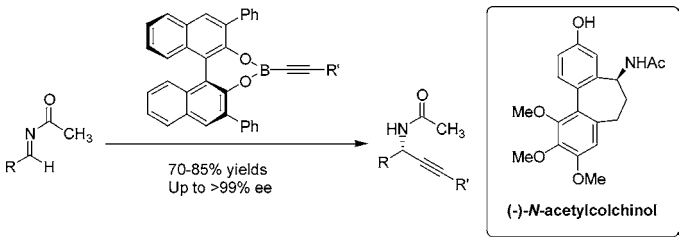
ABSTRACT



Alkynylboronates derived from 3,3′-disubstituted-2,2′-binaphthols react with various *N*-acylimines to give the expected chiral propargylamides with up to 99% ee. This new methodology was applied to the first enantioselective synthesis of the antitubulin agent (–)-*N*-acetylcolchinol.

Stereochemically defined propargylamides are important as synthetic intermediates for the preparation of natural products[1] and biologically active compounds.[2] Therefore, there is considerable interest in the preparation of these amides. Typical routes to prepare chiral propargylamides include metal complex (Cu,[3] Zn, and Zr[4]) catalyzed terminal alkyne addition to achiral imines or the addition of alkynylmetallics to imines bearing chiral auxiliaries.[5] Protecting groups or auxiliaries are then removed, and the intermediate propargylamines are acylated to provide the desired propargylamides.

However, to our knowledge, a method that provides reliable and direct access to enantiomerically enriched propargylamides via asymmetric synthesis has not been reported.[6]

Recently, we found that 3,3′-disubstituted binaphthol-modified alkynylboronates could deliver alkynyl groups onto enones in a conjugate fashion with excellent yields (up to 99%) and enantioselectivities (up to >99% ee).[7] Here we report an asymmetric synthesis of *N*-protected propargylamines by alkynylation of *N*-acylimines. We reasoned that *N*-acylimines (**1**, Scheme 1), being structurally similar to enones in that they also bear a carbonyl group conjugated with a double bond (C═N instead of C═C), might also react

(1) For recent examples, see: (a) Trost, B. M.; Chung, C. K.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 4327−4329. (b) Davidson, M. H.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 1601−1603. (c) Brennan, C. J.; Pattenden, G.; Rescourio, G. *Tetrahedron Lett.* **2003**, *44*, 8757−8760.

(2) Osipov, S. N.; Tsouker, P.; Hennig, L.; Bergur, K. *Tetrahedron* **2004**, *60*, 271−274.

(3) For representative examples, see: (a) Knopfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971−5973. (b) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324−2325. (c) Wei, C.; Mague, J. T.; Li, C. J. *Proc. Nat. Acad. Sci.* **2004**, 5749−5754. (d) Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron Lett.* **2004**, *45*, 8705−8706.

(4) Travers, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273−3275.

(5) For representative examples, see: (a) Lettan, R. B.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 3227−3230. (b) Bonanni, M.; Marradi, M.; Cicchi, S.; Faggi, C.; Goti, A. *Org. Lett.* **2005**, *7*, 319−322. (c) Dondoni, A.; Perrone, D. *Tetrahedron* **2003**, *59*, 4261−4273. (d) Fassler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054−3056. (e) Feuvrie, C.; Blanchet, J.; Bonin, M.; Micouin, L. *Org. Lett.* **2004**, *6*, 2333−2336.

(6) Recent examples of racemic syntheses of propargylamides: (a) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497−1499. (b) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107−1110 and references therein.

(7) Chong, J. M.; Shen, L.; Taylor, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 1822−1823.

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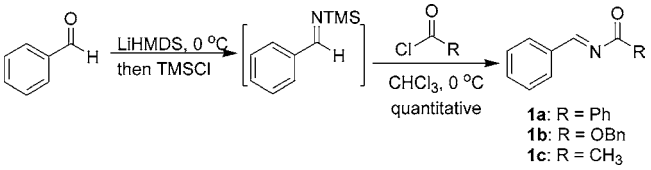
Scheme 1. Syntheses of *N*-Acylbenzaldimines

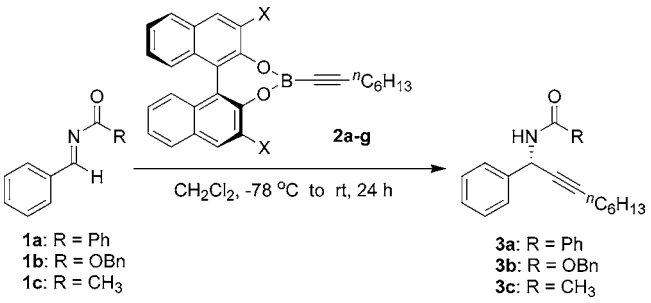


with alkynylboronates in a 1,4-addition manner to give chiral propargyl amides.

Following Kupfer's procedure,[8] *N*-acylbenzaldimines (**1a**−**c**) were synthesized in one pot from benzaldehyde quantitatively (Scheme 1). Since **1a**−**c** are very moisture-sensitive compounds, they were used directly without further purification.

Upon treating **1a** with binaphthol-modified alkynylboronate **2a** in CH_2Cl_2, the desired chiral propargylbenzamide **3a** was obtained in 84% yield with 64% ee. Other solvents (toluene, THF, ether) gave slightly lower selectivities. Further investigation showed that when 3,3′-disubstitutedbinaphthols were used in place of the parent binaphthol, additions to **1** were considerably more selective (Table 1).

Table 1. Alkynylation of *N*-Acylbenzaldimines with Alkynylboronates

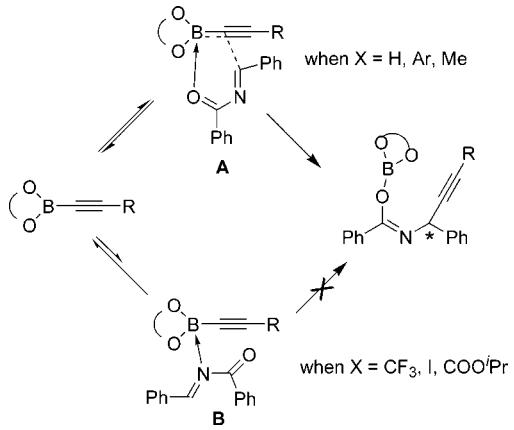


	reagent				
entry	X	compd	R	yield[a] (%)	ee[b] (%)
1	H	**2a**	Ph	84	64
2	Me	**2b**	Ph	85	67
3	I	**2c**	Ph	30	80
4	CF_3	**2d**	Ph	<20	75
5	COO^iPr	**2e**	Ph	<20	nd[c]
6	Ph	**2f**	Ph	82	80
7	4-$MeOC_6H_4$	**2g**	Ph	84	80
8	I	**2c**	OBn	40	80
9	Ph	**2f**	OBn	90	40
10	I	**2c**	CH_3	33	94
11	Ph	**2f**	CH_3	75	92

[a] Isolated yields of purified products based on chiral boronates (acylimines were generated in situ without isolation). [b] Determined by HPLC analysis with a Chiralcel OD column. [c] Not determined.

Among a variety of boronates, 3,3′-diarylbinaphthol-modified boronates (**2f**, **2g**) gave the best results in terms of yield and selectivity. *N*-Acetylimine **1c** gave the best ee's among the three acylimines. The iodo-substituted binaphthol **2c**, which is also the best ligand for catalytic conjugate alkynylation of enones,[9] gave excellent ee's (Table 1, entries 3, 8, and 10). However, the yields were poor. In fact all boronates with relatively strong electron-withdrawing groups on the binaphthol rings gave poor yields (Table 1, entries 3−5, 8, and 10). This result may be rationalized by proposing that, to deliver the alkynyl group via a 1,4-fashion, alkynyl boronates must coordinate with the oxygen atom of the acylimines (Scheme 2). Electron-withdrawing groups (I, CF_3, COO^iPr) increase the Lewis acidity of boronates and thus increase the possibility of boron coordinating with the nitrogen atom of the acylimine, leading to poor yields. We have no experimental evidence for this coordination, but it is offered as a speculation as to why electron-withdrawing groups have a major negative impact on reactions of alkynylboronates with acylimines but not on the analogous reactions with enones.[9]

Scheme 2. Alkynylation of *N*-Benzoylbenzaldimine with Alkynylboronates



Alkynylation of other *N*-acetylimines using **2f** and **2h** proceeded smoothly to give products in high yields (Table 2). Excellent enantioselectivities (>90% ee) were observed for all of the aromatic imines examined (Table 2, entries 1−6, 8, and 9) with highest selectivities (99% ee) noted for aromatic groups that are ortho substituted (Table 2, entries 5 and 6). Similar to the results from our previous study on allylboration,[10] high yields but lower selectivity were found with an alkenylimine (Table 2, entry 7). However, with a larger alkenyl group, excellent selectivity was obtained (Table 2, entry 10). Aliphatic acylimines were not examined as the method of preparation used is applicable only to nonenolizable aldehydes.[8]

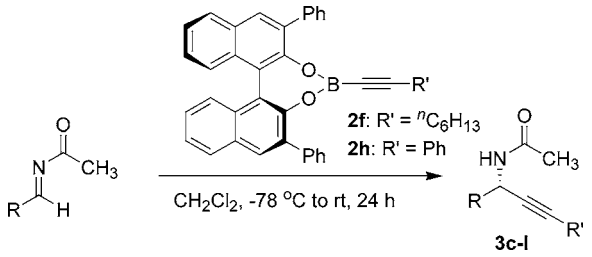
The adduct **3k** was prepared particularly to determine the absolute configuration of the addition products. (*S*)-Boronate

(8) (a) Kupfer, R.; Meier, S.; Wurtwein, E.-U. *Synthesis* **1984**, 688−690. (b) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289−294.

(9) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244−3245.

(10) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701−2704.

Table 2. Alkynylation of *N*-Acetylimines with **2f** and **2h**



entry	R	R′	compd	yield[a] (%)	ee[b] (%)
1	Ph	^{n}C$_6$H$_{13}$	**3c**	75	92
2	4-ClC$_6$H$_4$	^{n}C$_6$H$_{13}$	**3d**	72	91
3	4-MeOC$_6$H$_4$	^{n}C$_6$H$_{13}$	**3e**	81	92
4	4-MeC$_6$H$_4$	^{n}C$_6$H$_{13}$	**3f**	76	92
5	2-MeC$_6$H$_4$	^{n}C$_6$H$_{13}$	**3g**	78	99
6	1-naphthyl	^{n}C$_6$H$_{13}$	**3h**	70	>99[c]
7	PhCH=CH	^{n}C$_6$H$_{13}$	**3i**	75	67
8	Ph	Ph	**3j**	85	92
9	4-BrC$_6$H$_4$	Ph	**3k**	75	91
10	PhCH=C(CH$_3$)	Ph	**3l**	80	93

[a] Isolated yields of purified products based on chiral boronates (acylimines were generated in situ without isolation). [b] Determined by HPLC analysis with a Chiralcel OD column. [c] The minor enantiomer was not detected by HPLC analysis.

2h produced propargyl amide **3k** with *S* stereochemistry (X-ray). This stereochemical result may be explained using a cyclic six-membered chair transition state model similar to that proposed by us for additions of the same alkynylboronate reagents to enones (Figure 1).[7] In this model, the larger or

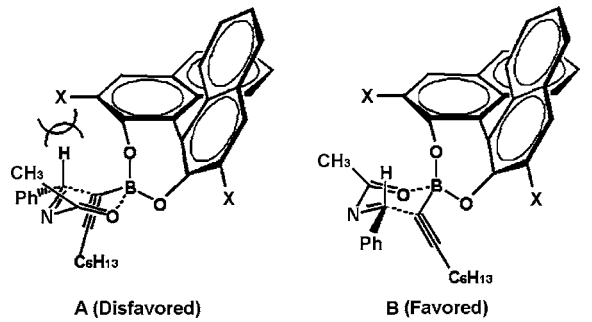


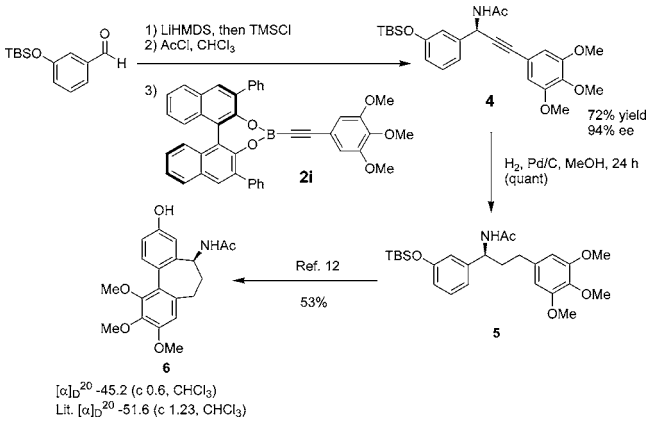
Figure 1. Proposed model.

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. The nonbonded interactions between the 3-substituent (Ph) and the axial imine hydrogen presumably favors **B** over **A** in the six-membered ring transition state.

This methodology was applied to the first enantioselective synthesis of (−)-*N*-acetylcolchinol **6**. It has been reported that the *O*-phosphate of (−)-*N*-acetylcolchinol **6**, also known as ZD6126, is useful in the treatment of cancer by selectively disrupting tumor vasculature, leading to vessel occlusion and extensive tumor necrosis.[11] Racemic *N*-acetylcolchinol has been prepared by total synthesis,[12] but (−)-*N*-acetylcolchinol has been previously obtained only by degradation of natural colchicine.[11,13]

The synthesis began with conversion of TBS protected 3-hydroxybenzaldehyde to its *N*-acetylimine. The crude imine was treated with (*R*)-diphenylbinaphthol alkynylboronate **2i** to give the desired (*R*)-acetamide **4** in 72% yield and 94% ee. (On the basis of the reaction model proposed, (*R*)-diphenylbinaphthol should give the natural enantiomer of the final product, whereas (*S*)-diphenylbinaphthol would give the other enantiomer.) After hydrogenation over Pd/C, the saturated compound (*S*)-**5** was obtained in quantitative yield. Finally, following Sawyer's procedure,[12] (*S*)-**5** was transformed into (−)-*N*-acetylcolchinol **6** by treatment with $(CF_3COO)_3Tl$ in the presence of freshly distilled $BF_3{\cdot}OEt_2$, TFA, and TFAA in an unoptimized yield of 53%. This material exibited an optical rotation of $[\alpha]^{20}_D$ −45.2 (*c* 0.6, $CHCl_3$), which is comparable to the literature value for (−)-*N*-acetylcolchinol obtained from degradation of (−)-colchicine (Scheme 3).[13]

Scheme 3. Total Synthesis of (−)-*N*-Acetylcolchinol



In summary, we have shown that 3,3′-disubstituted binaphthol-modified alkynylboronates can be used to prepare chiral propargylamides in high yields and enantioselectivities. This represents the first direct asymmetric synthesis of propargylamides. We are currently investigating the catalytic alkynylation of acylimines and other conjugate addition

(11) (a) Davis, P. D.; Dougherty, G. J.; Blakey, D. C.; Galbraith, S. M.; Tozer, G. M.; Holder, A. L.; Naylor, M. A.; Nolan, J.; Stratford, M. R. L.; Chaplin, D. J.; Hill, S. A. *Cancer Res.* **2002**, *62*, 7247−7253. (b) Micheletti, G.; Pli, M.; Borsotti, P.; Martinelli, M.; Imberti, B.; Taraboletti, G.; Giavazzi, R. *Cancer Res.* **2003**, *63*, 1534−1537. (c) Bergemann, S.; Brecht, R.; Buttner, F.; Guenard, D.; Gust, R.; Seitz, G.; Stubbs, M. T.; Thoret, S. *Bioorg. Med. Chem.* **2003**, *11*, 1269−1281. (d) Vorogushin, A. V.; Predeus, A. V.; Wulff, W. D.; Hansen, H. J. *J. Org. Chem.* **2003**, *68*, 5826−5831.

(12) (±)-**6** was prepared in 71% yield using this method: (a) Sawyer, J. S.; Macdonald, T. L. *Tetrahedron Lett.* **1988**, *29*, 4839−4842.

(13) Cech, J.; Santavy, F. *Collect. Czech. Chem. Commun.* **1949**, *14*, 532−539.

acceptors, as well as applications of this methodology in total synthesis. These results will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data for propargylamides (**3a**−**l**, **4**−**6**), and X-ray data for **3k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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