ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 12234–12236

www.rsc.org/chemcomm

COMMUNICATION

Catalytic enantioselective addition of terminal 1,3-diynes to *N*-sulfonyl aldimines: access to chiral diynylated carbinamines†

Tian-Lin Liu,[a] Heng-Xia Zhang,[a] Yan Zheng,[a] Qingwei Yao[b] and Jun-An Ma*[a]

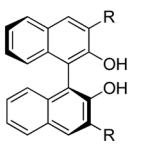
Received 6th October 2012, Accepted 30th October 2012
DOI: 10.1039/c2cc37290h

An efficient method for the asymmetric synthesis of chiral diynylated carbinamines is described. The direct catalytic enantioselective addition of terminal 1,3-diynes to *N*-sulfonyl aldimines proceeded smoothly under mild reaction conditions to produce diynylated carbinamines in up to 98% yield and 99% ee.

Chiral propargyl amines are potentially intriguing blocks for the synthesis of many natural products and compounds of pharmaceutical significance.[1] The asymmetric alkynylation of imines provides the most direct access to these important synthetic intermediates.[2] Since the pioneering work of both Li's and Knochel's groups on the catalytic asymmetric addition of terminal alkynes to imines and their analogues,[3] significant progress has been made in the development of highly selective and efficient catalytic systems for these synthetically useful transformations.[4] However, little attention has been paid to exploring 1,3-diynes as viable nucleophilic substrates in the asymmetric addition reaction of imines.[5] Such studies would be of immense benefit for expanding the scope of application of this reaction to the synthesis of chiral diynylated carbinamines.[6] Herein we report the results of our preliminary investigation of enantioselective diynylation of aldimines by using various terminal 1,3-diynes. We demonstrate that, in the presence of binol-type ligands, the present transformation provides a facile route to chiral diynylated carbinamines in high yield (up to 98%) and excellent enantioselectivity (up to 99% ee).

In an initial investigation, we conducted the model reaction of *N*-tosyl benzaldimine **1a** with diynylzinc generated *in situ* from phenylbuta-1,3-diyne **2a** and Me_2Zn, by employing (*S*)-1,1′-bi-2-naphthol (binol) as the chiral ligand to afford the desired adduct **3aa** in 77% yield but with poor enantioselectivity (8% ee) (entry 1, Table 1). Subsequent screening with a series of binol-type ligands containing various groups at the 3,3′-positions of the binaphthol backbone (entries 2–10) revealed the bulky ligand **L8** to be optimal, delivering adduct **3aa** in 90% yield with high enantioselecitivity (92% ee), whereas the use of more bulky ligands **L9** and **L10** resulted in a substantial decrease in enantioselectivity (entries 9 and 10 *vs.* 8). A comparison of the results obtained in different solvents showed that this asymmetric addition is not sensitive to the solvent used (entries 8 and 11–13). Given the poor solubility of *N*-sulfonyl aldimines in toluene and ether, we chose dichloroethane (DCE) as the reaction solvent. Decreasing the amount of ligand to 15 mol% resulted in a decrease in both the yield and the ee value of the product (entry 14). Further optimization by changing the temperature and the reaction time (entries 15 and 16) revealed that the best results were obtained when 20 mol% of ligand **L8** was used at room temperature for 6 hours (96% yield, 94% ee).

Table 1 Optimization of reaction conditions[a]



L1 R = H **L6** R = 4-PhC_6H_4
L2 R = I **L7** R = 4-$NO_2C_6H_4$
L3 R = Br **L8** R = 3,5-$(CF_3)_2C_6H_3$
L4 R = $SiMe_3$ **L9** R = 4-[3,5-$(CF_3)_2C_6H_3$]C_6H_4
L5 R = C_6H_5 **L10** R = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$

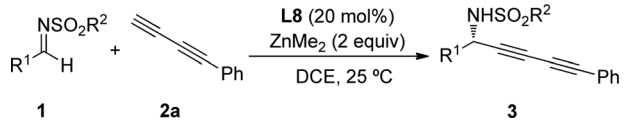
Entry	Ligand (mol%)	Solvent	Yield[b] (%)	ee[c] (%)
1	**L1** (20)	Toluene	77	8
2	**L2** (20)	Toluene	81	72
3	**L3** (20)	Toluene	87	87
4	**L4** (20)	Toluene	74	15
5	**L5** (20)	Toluene	80	25
6	**L6** (20)	Toluene	67	31
7	**L7** (20)	Toluene	82	40
8	**L8** (20)	Toluene	90	92
9	**L9** (20)	Toluene	81	56
10	**L10** (20)	Toluene	80	58
11	**L8** (20)	Et_2O	82	89
12	**L8** (20)	DCM	88	91
13	**L8** (20)	DCE	94	93
14	**L8** (15)	DCE	88	85
15[d]	**L8** (20)	DCE	85	90
16[e]	**L8** (20)	DCE	96	94

[a] Reactions were conducted with 1 equiv. of **1a**, 2.2 equiv. of **2a**, 2 equiv. of Me_2Zn (1.2 M in toluene), and the ligand in solvent at room temperature. [b] Yield of isolated products. [c] The ee values were determined by HPLC analysis on a chiral stationary phase. [d] Reaction temperature: 10 °C. [e] Reaction time: 6 h.

[a] *Department of Chemistry, Tianjin University, Tianjin 300072, China. E-mail: majun_an68@tju.edu.cn; Fax: +86-22-2740-3475*
[b] *Sphinx Scientific Laboratory Corporation, Sycamore, IL 60178, USA*

† Electronic supplementary information (ESI) available. CCDC 870991. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc37290h

Table 2 Enantioselective addition of phenylbuta-1,3-diyne **2a** to various *N*-sulfonyl aldimines **1**[a]



1 **2a** **3**

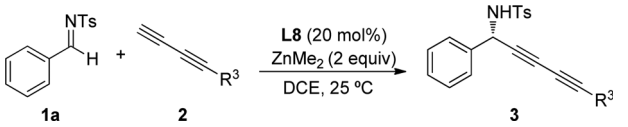
Entry	**1**: R^1, R^2	Time (h)	**3**: Yield[b]	ee[c] (%)
1	**1a**: Phenyl, 4-tolyl	6	**3aa**: 96	94
2	**1b**: 4-Fluorophenyl, 4-tolyl	5	**3ba**: 89	97
3	**1c**: 4-Chlorophenyl, 4-tolyl	8	**3ca**: 93	91
4	**1d**: 4-Bromophenyl, 4-tolyl	4	**3da**: 91	98
5	**1e**: 4-Methylphenyl, 4-tolyl	8	**3ea**: 93	98
6	**1f**: 4-Methoxyphenyl, 4-tolyl	4	**3fa**: 90	96
7	**1g**: 3-Methoxyphenyl, 4-tolyl	6	**3ga**: 93	94
8	**1h**: 2-Chlorophenyl, 4-tolyl	16	**3ha**: 91	94
9	**1i**: 2-Bromophenyl, 4-tolyl	16	**3ia**: 90	95
10	**1j**: 2-Allylphenyl, 4-tolyl	16	**3ja**: 91	92
11	**1k**: 3,4-Dichlorophenyl, 4-tolyl	8	**3ka**: 94	90
12	**1l**: 2,4,6-Trimethoxyphenyl, 4-tolyl	12	**3la**: 93	91
13	**1m**: 2-Naphthyl, 4-tolyl	16	**3ma**: 93	92
14	**1n**: 2-Furyl, 4-tolyl	5	**3na**: 90	96
15	**1o**: Cinnamyl, 4-tolyl	4	**3oa**: 95	91
16	**1p**: Phenyl, cyclopropyl	8	**3pa**: 93	90
17	**1q**: Phenyl, 1-allylcyclopropyl	8	**3qa**: 91	90
18[d]	**1r**: CF_3, 4-tolyl	8	**3ra**: 74	61
19[d]	**1s**: $CH_3(CH_2)_2$, 4-tolyl	8	**3sa**: 74	63

[a] General reaction conditions: **1**/**2a**/Me_2Zn/**L8** = 1.0 : 2.2 : 2.0 : 0.2 in DCE at room temperature for the stated time. [b] Yield of isolated products. [c] The ee values were determined by HPLC analysis on a chiral stationary phase. [d] Ligand **L10** was used.

With the optimal conditions established, the scope of the reaction was then probed. As highlighted in Table 2, a wide range of functional groups, including electron-neutral, -withdrawing, and -donating groups on the aromatic rings of *N*-tosyl benzaldimines can be tolerated (Table 2, entries 1–12). In all cases, high yields (90–96%) and excellent ee values (90–98%) were obtained. The reaction worked well with *N*-tosyl-2-naphthaldimine **1m** to afford the adduct **3ma** in 93% yield with 92% ee (entry 13). Other aromatic imine derivatives such as *N*-tosyl-2-furaldimine **1n** also worked well, furnishing the corresponding product **3na** in high yield and enantioselectivity (entry 14). It was worth noting that *N*-tosyl cinnamaldimine **1o** gave the 1,2-adduct **3oa** in 95% yield with 91% ee (entry 15). To further define the scope of our methodology, the addition reactions of different *N*-sulfonyl-substituted benzaldimines such as **1p** and **1q** were also tested (entries 16 and 17). The desired adducts **3pa** and **2qa** were obtained in high yields and enantioselectivities. In addition, we investigated the addition reaction with alkyl-substituted imines. These substrates were found to give good yields and moderate ee values. For example, in the presence of more bulky ligand **L10**, *N*-tosyl-2,2,2-trifluoroacetaldimines **1r** and **1s** provided the adducts **3ra** and **3sa** in good yields with 61% ee and 63% ee, respectively (entries 18 and 19).[7]

This protocol can also be readily extended to the use of other 1,3-diynes. As shown in Table 3, a series of representative substituted phenylbuta-1,3-diynes (**2b–i**) were shown to undergo the addition transformation with consistently high yields and enantioselectivities (entries 1–8). Both electron-withdrawing (F, Cl, Br) and electron-donating (Me, OMe) substituents at

Table 3 Enantioselective addition of various 1,3-diynes **2** to *N*-tosylaldimine **1a**[a]



1a **2** **3**

Entry	**2**: R^3	Time (h)	**3**: Yield[b] (%)	ee[c] (%)
1	**2b**: 4-Fluorophenyl	16	**3ab**: 92	90
2	**2c**: 4-Chlorophenyl	4	**3ac**: 95	95
3	**2d**: 4-Bromophenyl	4	**3ad**: 97	90
4	**2e**: 4-Methylphenyl	5	**3ae**: 95	93
5	**2f**: 4-Methoxyphenyl	3	**3af**: 98	97
6	**2g**: 2-Methoxyphenyl	4	**3ag**: 90	93
7	**2h**: 2-Chlorophenyl	16	**3ah**: 88	90
8	**2i**: 3-Methoxyphenyl	16	**3ai**: 93	88
9	**2j**: 1-Cyclohexenyl	6	**3aj**: 97	95
10	**2k**: Triisopropylsilyl	24	**3ak**: 95	93
11	**2l**: $TMSO(CH_3)_2CH$	3	**3al**: 90	92
12	**2m**: $C_6H_4CH_2CH_2$	8	**3am**: 94	>99

[a] General reaction conditions: **1**/**2a**/Me_2Zn/**L8** = 1.0 : 2.2 : 2.0 : 0.2 in DCE at room temperature for the stated time. [b] Yield of isolated products. [c] The ee values were determined by HPLC analysis on a chiral stationary phase.

various positions of the phenyl ring were well tolerated. One of the diynylated carbinamines (**3ad**) was crystallized from CH_2Cl_2–hexane, and its absolute configuration was determined to be *S* from single-crystal X-ray structural analysis (Fig. 1).[8] It is noteworthy that 1-cyclohexenyl- and triisopropylsilyl-substituted buta-1,3-diynes (**2j** and **2k**) also gave the adducts (**3aj** and **3ak**) in excellent yields and enantioselectivities (entries 9 and 10). Additionally, the reaction worked well with alkyl-substituted 1,3-diynes such as **2l** and **2m** to afford the desired products (**3al** in 90% yield and 92% ee, and **3am** in 94% yield and 99% ee) (entries 11 and 12).

Adducts **3** are versatile synthetic intermediates and can be readily transformed into functionalized amine derivatives that are otherwise difficult to access. For example, direct hydrogenation of **3aa** in the presence of 10% Pd/C in ethanol provided the secondary *N*-tosyl carbinamine **4**, in almost quantitative yield without any erosion of its enantiopurity, which can be conveniently converted to the corresponding free amine **5** by reductive cleavage with SmI_2 (Scheme 1).[9] Reduction of **3aa** with $LiAlH_4$ delivered the (*E*)-1, 3-enynyl-substituted carbinamine **6** in 85% yield with 94% ee.[10]

In summary, we have developed an efficient catalytic asymmetric diynylation of *N*-sulfonyl aldimines by using chiral binol-type ligands. The addition reaction proceeded smoothly under mild conditions for a broad variety of *N*-sulfonyl aldimines and terminal 1,3-diynes, affording the desired products in good to excellent yields (74–98%) and enantioselectivities (up to 99% ee). Further

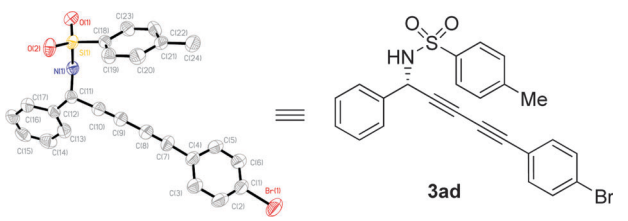
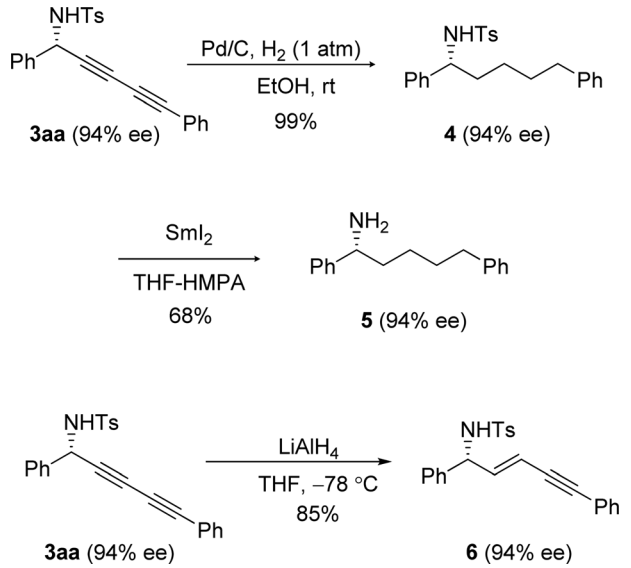


Fig. 1 X-ray crystal structure of the diynylated adduct **3ad** (ORTEP).



Scheme 1 Further synthetic transformations of the diynylated adduct **3aa**.

extension of this diynylation addition to other substrates is ongoing in our laboratory.

This work was supported financially by NSFC (No. 20902067 and 20972110).

Notes and references

1 For selected examples, see: (*a*) A. Hoepping, K. M. J. George, J. Flippen-Anderson and A. P. Kozikowski, *J. Med. Chem.*, 2000, **43**, 2064; (*b*) J. L. Wright, T. F. Gregory, S. P. Kesten, P. A. Boxer, K. A. Serpa, L. T. Meltzer, L. D. Wise, S. A. Espitia, C. S. Konkoy, E. R. Whittemore and R. M. Woodward, *J. Med. Chem.*, 2000, **43**, 3408; (*c*) G. S. Kauffman, G. D. Harris, R. L. Dorow, B. R. P. Stone, J. R. L. Parsons, J. A. Pesti, N. A. Magnus, J. M. Fortunak, P. N. Confalone and W. A. Nugent, *Org. Lett.*, 2000, **2**, 3119; (*d*) B. Jiang and M. Xu, *Angew. Chem., Int. Ed.*, 2004, **43**, 2543; (*e*) J. J. Fleming and J. Du Bois, *J. Am. Chem. Soc.*, 2006, **128**, 3926.

2 For selected reviews, see: (*a*) G. Alvaro and D. Savoia, *Synlett*, 2002, 651; (*b*) A. Job, C. F. Janeck, W. Bettray, R. Peters and D. Enders, *Tetrahedron*, 2002, **58**, 2253; (*c*) P. Zhou, B. Chen and F. A. Davis, *Tetrahedron*, 2004, **60**, 8003; (*d*) G. K. Friestad, *Eur. J. Org. Chem.*, 2005, 3157; (*e*) T. Vilaivan, W. Bhanthumnavin and Y. Sritana-Anant, *Curr. Org. Chem.*, 2005, **9**, 1315; (*f*) L. Zani and C. Bolm, *Chem. Commun.*, 2006, 4263; (*g*) G. K. Friestad and A. K. Mathies, *Tetrahedron*, 2007, **63**, 2541. For selected early examples of asymmetric alkynylations *via* addition of organometallics to chiral imines, see: (*h*) T. Fujisawa, M. Nagai, Y. Koike and M. Shimizu, *J. Org. Chem.*, 1994, **59**, 5865; (*i*) P. Merino, S. Anoro, E. Castillo, F. Merchan and T. Tejero, *Tetrahedron: Asymmetry*, 1996, **7**, 1887; (*j*) P. Merino, S. Anoro, E. Castillo, F. Merchan and T. Tejero, *Tetrahedron: Asymmetry*, 1997, **8**, 3489; (*k*) M. A. Huffman, N. Yasuda, A. E. Decamp and E. J. J. Grabowski, *J. Org. Chem.*, 1995, **60**, 1590.

3 (*a*) C. Wei and C.-J. Li, *J. Am. Chem. Soc.*, 2002, **124**, 5638; (*b*) C. Koradin, K. Polborn and P. Knochel, *Angew. Chem., Int. Ed.*, 2002, **41**, 2535; (*c*) N. Gommermann, C. Koradin, K. Polborn and P. Knochel, *Angew. Chem., Int. Ed.*, 2003, **42**, 5763; (*d*) C. Wei, J. T. Mague and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5749.

4 For a recent highlight, see: (*a*) P. de Armas, D. Tejedor and F. García-Tellado, *Angew. Chem., Int. Ed.*, 2010, **49**, 1013. For several recent examples, see: (*b*) F. Colombo, M. Benaglia, S. Orlandi, F. Usuelli and G. Celentano, *J. Org. Chem.*, 2006, **71**, 2064; (*c*) T.-R. Wu and J.-M. Chong, *Org. Lett.*, 2006, **8**, 15; (*d*) A. Z. Gonzalez, E. Canales and J. A. Soderquist, *Org. Lett.*, 2006, **8**, 3331; (*e*) W. Wei, M. Kobayashi, Y. Ukaji and K. Inomata, *Chem. Lett.*, 2006, 176; (*f*) Z. Shao, J. Wang, K. Ding and A. S. C. Chan, *Adv. Synth. Catal.*, 2007, **349**, 2375; (*g*) Z. Sun, S. Yu, Z. Ding and D. Ma, *J. Am. Chem. Soc.*, 2007, **129**, 9300; (*h*) M. Rueping, A. P. Antonchick and C. Brinkmann, *Angew. Chem., Int. Ed.*, 2007, **46**, 6903; (*i*) L. Zani, T. Eichhorn and C. Bolm, *Chem.–Eur. J.*, 2007, **13**, 2587; (*j*) M. Irmaka and M. M. K. Boysena, *Adv. Synth. Catal.*, 2008, **350**, 403; (*k*) G. Blay, L. Cardona, E. Climent and J. R. Pedro, *Angew. Chem., Int. Ed.*, 2008, **47**, 5593; (*l*) Y. Lu, T. C. Johnstone and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2009, **131**, 11284; (*m*) G. Huang, J. Yang and X. Zhang, *Chem. Commun.*, 2011, **47**, 5587.

5 For asymmetric diynylation of aldehydes, see: (*a*) S. Reber, T. F. Knöfel and E. M. Carreira, *Tetrahedron*, 2003, **59**, 6813; (*b*) B. M. Trost, V. S. Chan and D. Yamamoto, *J. Am. Chem. Soc.*, 2010, **132**, 5186; (*c*) M. Turlington, Y. Du, S. G. Ostrum, V. Santosh, K. Wren, T. Lin, M. Sabat and L. Pu, *J. Am. Chem. Soc.*, 2011, **133**, 11780; (*e*) E. R. Graham and R. R. Tykwinski, *J. Org. Chem.*, 2011, **76**, 6574.

6 For asymmetric diynylation of trifluoromethyl ketones and ketimines, see: (*a*) K. Aikawa, Y. Hioki and K. Mikami, *Org. Lett.*, 2010, **12**, 5716; (*b*) T.-L. Liu, H. Ma, F.-G. Zhang, Y. Zheng, J. Nie and J.-A. Ma, *Chem. Commun.*, 2011, **47**, 12873; (*c*) F.-G. Zhang, H. Ma, J. Nie, Y. Zheng, Q. Gao and J.-A. Ma, *Adv. Synth. Catal.*, 2012, **354**, 1422; (*d*) F.-G. Zhang, H. Ma, Y. Zheng and J.-A. Ma, *Tetrahedron*, 2012, **68**, 7663. To the best of our knowledge, there is no direct catalytic asymmetric synthesis of chiral diynylated carbinamines. For the synthesis of diynyl-containing chiral carbinamines *via* the coupling reaction of terminal alkynes, see: (*e*) E. Ko, J. Liu, L. M. Perez, G. Lu, A. Schaefer and K. Burgess, *J. Am. Chem. Soc.*, 2011, **133**, 462.

7 The ligand effect on the addition of phenylbuta-1,3-diyne to *N*-tosyl 2,2,2-trifluoroacetaldimine to afford the adduct: **L8** (64% yield, 35% ee), **L9** (77% yield, 43% ee), and **L10** (74% yield, 61% ee).

8 CCDC 870991 (**3ad**)†.

9 Unfortunately, due to the presence of the conjugated diyne and enyne moieties in compounds **3aa** and **6**, all attempts to remove the N–Ts group under reductive conditions failed to give the free amines. For similar observations, see ref. 4*k*.

10 For the synthesis of similar enynyl-substituted carbinamines, see: J.-R. Kong, C.-W. Cho and M. J. Krische, *J. Am. Chem. Soc.*, 2005, **127**, 11269.

