Asymmetric Catalysis

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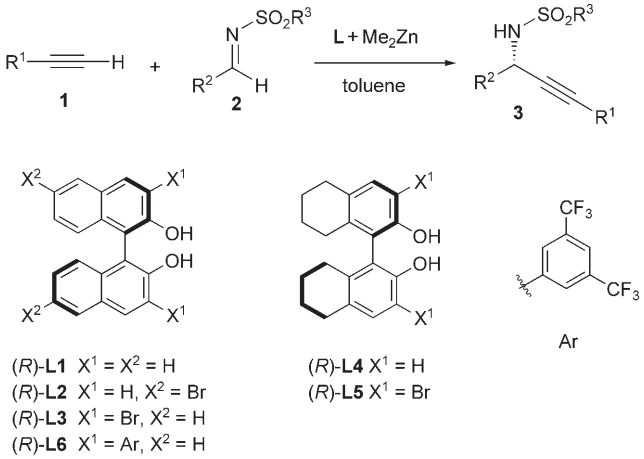
Highly Enantioselective Zinc/Binol-Catalyzed Alkynylation of *N*-Sulfonyl Aldimines**

*Gonzalo Blay, Luz Cardona, Estela Climent, and José R. Pedro**

The catalytic enantioselective formation of new C–C bonds is an important class of organic reactions.[1] Among them, the asymmetric additions of terminal alkynes to C=O and C=N bonds are two of the most important objectives in organic synthesis; the resulting chiral propargylic alcohols and amines are versatile building blocks for the synthesis of a wide range of natural products and pharmaceuticals. Some excellent work has been reported on the asymmetric addition of alkynes to carbonyl compounds resulting in high *ee* values.[2] However, the practical enantioselective alkynylation of imines and imine derivatives to form propargylic amines is challenging because of the poor electrophilicity of the azomethine carbon.[3] In this context, most of the studies reported so far deal with the catalytic enantioselective alkynylation of *N*-aryl imines by using Cu^I salts in combination with nitrogen-containing ligands. The leading studies of this reaction with *N*-aryl imines have been developed by Wei et al.,[4] Bisai and Singh,[5] and Benaglia and co-workers[6]; and Knochel and co-workers[7] and Carreira and co-workers[8] reported using iminium intermediates generated in situ in a three-component synthesis of propargylic amines.[9] Other methods, which do not make use of copper complexes as the catalyst, have also been described. Hoveyda and co-workers have used peptide-based ligands in combination with Zr-(O*i*Pr)$_4$·HO*i*Pr to catalyze the addition of preformed mixed alkynylzinc reagents to various *N*-aryl aromatic imines, which gives good results with trimethylsilylethyne and lower enantioselectivities with aryl-substitued alkynes.[10] Jiang and Si have described the addition of alkynes to a trifluoromethyl activated cyclic imine by using a stoichiometric amount of a chiral amino alcohol ligand.[11] Recently, Bolm and co-workers have described the use of dimethylzinc to catalyze the addition of terminal alkynes to *N*-aryl and *N*-protected imines in the absence of ligands.[12] An enantioselective version has been implemented by these authors for *o*-methoxyaniline-derived imines by using a relatively large loading (40 mol%) of the amino alcohol ligands.[13] In contrast, *N*-acyl- and *N*-sulfonyl-protected imines show enhanced reactivity because of the electron-withdrawing character of the protecting group. The alkynylation of these substrates lead to protected propargylic amines. The highly enantioselective alkynylation of *N*-acyl imines has been carried out by using chiral alkynylboronates[14] and alkynylboranes,[15] which are based on the binol and the borabicyclo[3.3.2]decane scaffolds, respectively, as reagents. However, to the best of our knowledge, the enantioselective alkynylation of *N*-tosyl imines has not been reported so far. Because of the increased reactivity of *N*-sulfonyl imines and the findings reported by Bolm and co-workers,[12] we envisioned a dimethylzinc-mediated catalytic enantioselective alkynylation of *N*-sulfonyl imines by using an appropriate ligand (Scheme 1). Binol-type ligands were chosen in our study because they are known to give highly enantioselective reactions with a variety of metals, including zinc.[16]



Scheme 1. Alkynylation of *N*-sulfonyl imines (top) and binol-type ligands used in this study (bottom).

To optimize the reaction conditions, we used the asymmetric reaction of phenylacetylene (**1a**: R^1 = Ph) with *N*-tosyl benzaldimine (**2a**, R^2 = Ph, R^3 = 4-tolyl). Initially, the reaction was conducted by using 0.2 equivalents of (*R*)-binol (**L1**), 2 M Me_2Zn in toluene (6 equiv), and phenylacetylene (7.2 equiv) in toluene (2 mL) at room temperature. These reaction conditions are very similar to those reported by Chan and co-workers[17] and by our group[18] for the enantioselective alkynylation of aldehydes catalyzed by chiral amino alcohol and mandelamide ligands, respectively. Under these conditions the reaction was complete after 5 hours to give product **3aa** in good yield (80%), but with a low enantiomeric excess (8%) (Table 1, entry 1). Next, we screened other binol-type ligands (**L2**–**L5**) which contained electron-withdrawing

[*] Dr. G. Blay, Dr. L. Cardona, E. Climent, Prof. Dr. J. R. Pedro
Departament de Química Orgànica, Facultat de Química
Universitat de València
Dr. Moliner 59, 46100 Burjassot (València) (Spain)
Fax: (+34) 963-544-328
E-mail: jose.r.pedro@uv.es

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Table 1: Enantioselective addition of phenylacetylene (**1a**, $R^1 = Ph$) to *N*-tosyl benzaldimine (**2a**, $R^2 = Ph$, $R^3 = 4$-tolyl). Screening of ligands and conditions.[a]

Entry	Ligand	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**L1**	5	80	8
2	**L2**	3	84	29
3	**L3**	3	90	93
4	**L4**	20	75	6
5	**L5**	4	73	66
6[d]	**L3**	23	79	78
7[e]	**L3**	6	70	68
8[f]	**L3**	4	70	62
9	**L6**	3	84	96
10[g]	**L3**	2	85	78
11[g]	**L6**	2.5	82	89

[a] See Scheme 1. **2a** (0.25 mmol), **L** (0.05 mmol), Me_2Zn (1.5 mmol), **1a** (1.8 mmol), Tol (2.75 mL), RT. [b] Yields of isolated product. [c] Determined by HPLC methods. [d] Reaction at 0°C. [e] **L3** (0.1 mmol). [f] Me_2Zn (3 mmol), **1a** (3.6 mmol). [g] Reaction carried out with tosyl imine **2f** ($R_2 = R_3 = 4$-tolyl).

groups at the 3,3′ and 6,6′ positions, as well as a tetrahydrogenated ring. Ligand **L3** (Table 1, entry 3), having bromide atoms at the 3,3′ positions, led to the best result (90% yield, 93% *ee*). This result is in accordance with that described by Wu and Chong[14] in which the substitutions at the 3,3′ positions on the binol-based alkynylboronates were essential for obtaining high enantioselectivities. We used **L3** to screen different temperatures and catalyst loadings. Lowering the temperature to 0°C had a negative effect on the enantioselectivity, resutling in 78% *ee* (Table 1, entry 6). With regard to the catalyst loading, a reduction to 10 mol% had deleterious effect on the reaction; compound **3aa** was obtained in 70% yield and 68% *ee* (Table 1, entry 7). However, an interesting increase in the enantioselectivity was obtained when the reaction was carried out in the presence of the highly hindered binol ligand **L6**. So, by using ligand **L6**, tosyl imine **2a** led to product **3aa** in 96% *ee* compared to the 93% *ee* obtained when the reaction was carried out with **L3** (Table 1, entry 9 versus 3). A greater increase in the enantioselectivity was observed with tosyl imine **2f** ($R^2 = R^3 = 4$-tolyl); in this case expected product **3af** was obtained with 89% *ee* by using **L6** and with 78% *ee* by using **L3** (Table 1, entry 11 versus 10).

Although tosyl imines are by far the most commonly used type of *N*-sulfonyl imines in organic synthesis, Carretero and co-workers[19] and Sugimoto et al.[20] have shown that the substitution at the sulfur atom can affect the chemical behavior of *N*-sulfonyl imine, influencing both the yield and the enantioselectivity of the reaction. Therefore, we tested the reaction with different benzaldehyde-derived *N*-sulfonyl imines (**2b–e**) (Table 2). All of the imines tested gave phenylacetylene addition products **3ab–ae** in similar yields (78–86%) and enantioselectivities (87–91% *ee*), with tosyl imine **2a** giving the best results (Table 2, entry 1).

The optimized conditions were used for the addition of phenylacetylene (**2a**) to several *N*-tosyl benzaldimines (Table 3, entries 1–4) with good results. However, we noted that the efficiency of the addition of phenylacetylene[12,13] and other dialkylzinc reagents to carbonyl groups[21] can be

Table 2: Enantioselective addition of phenylacetylene (**1a**, $R^1 = Ph$) to *N*-sulfonyl benzaldimines **2a–e** ($R^2 = Ph$).[a]

Entry	**2**	R^2	R^3	*t* [h]	**3**	Yield [%][b]	*ee* [%][c]
1	**2a**	Ph	*p*-$CH_3C_6H_4$	3	**3aa**	84	96
2	**2b**	Ph	*p*-$CH_3OC_6H_4$	4	**3ab**	86	90
3	**2c**	Ph	*p*-ClC_6H_4	3	**3ac**	82	89
4	**2d**	Ph	*p*-$NO_2C_6H_4$	3	**3ad**	78	87
5	**2e**	Ph	2-thienyl	3	**3ae**	82	91

[a] See Scheme 1. **2** (0.25 mmol), **L6** (0.05 mmol), Me_2Zn (1.5 mmol), **1a** (1.8 mmol), Tol (2.75 mL), RT. [b] Yields of isolated product. [c] Determined by HPLC methods.

Table 3: Enantioselective addition of phenylacetylene (**1a**, $R^1 = Ph$) to *N*-tosyl imines **2a,f–s** ($R^3 = 4$-tolyl).[a]

Entry	**2**	R^2	*t* [h]	**3**	Yield [%][b]	*ee* [%][c]
1	**2a**	Ph	3	**3aa**	85 (84)[d]	98 (96)[d]
2	**2f**	*p*-$CH_3C_6H_4$	2.5	**3af**	83 (82)[d]	92 (89)[d]
3	**2g**	*m*-$CH_3C_6H_4$	2.5	**3ag**	87 (89)[d]	95 (87)[d]
4	**2h**	*o*-$CH_3C_6H_4$	2.5	**3ah**	80 (85)[d]	99 (96)[d]
5	**2i**	*p*-$CH_3OC_6H_4$	3.5	**3ai**	77	87
6	**2j**	*p*-BrC_6H_4	3	**3aj**	86	>99
7	**2k**	*p*-FC_6H_4	3	**3ak**	86	90
8	**2l**	*o*-FC_6H_4	3	**3al**	78	88
9	**2m**	2-naphthyl	4	**3am**	81	84
10	**2n**	2-furyl	3	**3an**	74	91
11	**2o**	3-furyl	3	**3ao**	74	64
12	**2p**	2-thienyl	3.5	**3ap**	72	78
13	**2q**	3-thienyl	3.5	**3aq**	75	81
14	**2r**	$PhCH_2CH_2$	2	**3ar**	86	18
15	**2s**	Cy	2	**3as**	84	38

[a] See Scheme 1. **2** (0.125 mmol), **L6** (0.025 mmol), Me_2Zn (0.75 mmol), **1a** (0.9 mmol), tol (0.7 mL), RT; [b] Yields of isolated product. [c] Determined by HPLC methods. [d] Values in parentheses are those obtained by using reaction conditions as detailed in Table 2. Cy = cyclohexyl.

increased by working at higher concentrations; an additional improvement to our reaction was obtained when the solvent volume was reduced by 50% and **L6** was used. As shown in Table 3, when the reactions were run at a higher concentration, a number of representative *N*-tosyl arylaldimines underwent addition with consistently high enantioselectivities, regardless of their steric or electronic nature (87–100% *ee*, Table 3, entries 1–8). Both electron-withdrawing (F, Br) and electron-donating (Me, OMe) substituents, as well as *ortho*, *meta*, and *para* substitution, were well tolerated. Bulky tosyl imine **2m**, derived from 1-naphthylcarbaldehyde, gave a slightly lower *ee* value (84%) (Table 3, entry 9). A number of *N*-tosyl imines (**2n–q**) derived from heteroaromatic aldehydes were also suitable substrates, giving the corresponding propargylic sulfonylamides in good yields with *ee* values between 64 and 91% (Table 3, entries 10–13). Finally, alkyl-substituted imines reacted to give the corresponding products in good yields, but with low enantioselectivities (Table 3, entries 13–14).

Finally, the use of other alkynes in this reaction was studied (Table 4). 4-Phenyl-1-butyne (**1b**) reacted with a number of representative *N*-tosyl imines giving good yields and high enantiomeric excesses, which range from 87 to 100%

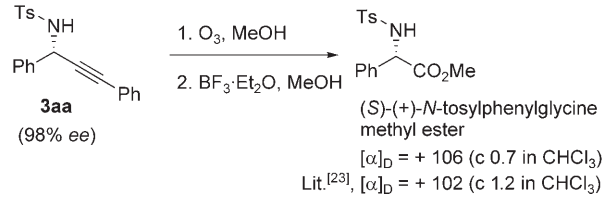
Table 4: Enantioselective addition of 4-phenyl-1-butyne (**1b**) and 1-hexyne (**1c**) to *N*-tosyl arylaldimines (R^3 = 4-tolyl).[a]

Entry	1	R^1	2	R^2	*t* [h]	3	Yield [%][b]	*ee* [%][c]
1	**1b**	$PhCH_2CH_2$	**2a**	Ph	4.5	**3ba**	75	89
2	**1b**	$PhCH_2CH_2$	**2f**	*p*-$CH_3C_6H_4$	4.5	**3bf**	80	93
3	**1b**	$PhCH_2CH_2$	**2j**	*p*-BrC_6H_4	5	**3bj**	70	>99
4	**1b**	$PhCH_2CH_2$	**2n**	2-naphthyl	5	**3bn**	74	87
5	**1b**	$PhCH_2CH_2$	**2o**	2-furyl	3	**3bo**	82	99
6	**1c**	$CH_3(CH_2)_3$	**2a**	Ph	6.5	**3ca**	82	81
7	**1c**	$CH_3(CH_2)_3$	**2f**	*p*-$CH_3C_6H_4$	7	**3cf**	70	89
8	**1c**	$CH_3(CH_2)_3$	**2j**	*p*-BrC_6H_4	7	**3cj**	70	93
9	**1c**	$CH_3(CH_2)_3$	**2n**	2-naphthyl	21	**3cn**	71	76
10	**1c**	$CH_3(CH_2)_3$	**2o**	2-furyl	6	**3co**	85	93

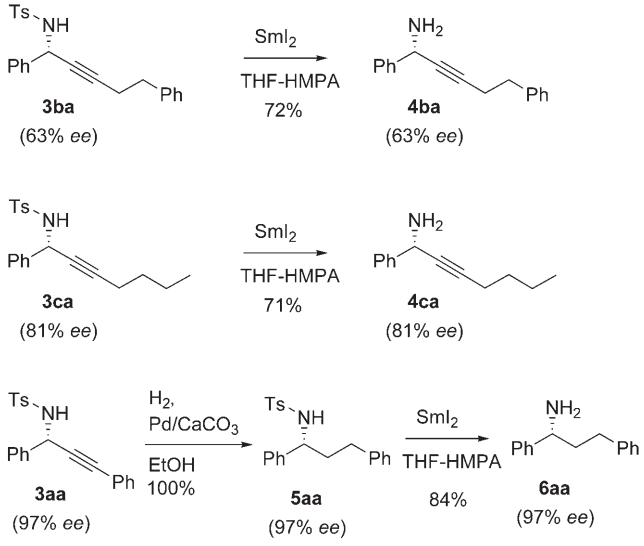
[a] See Scheme 1. **2** (0.125 mmol), **L6** (0.025 mmol), Me_2Zn (0.75 mmol), **1a** (0.9 mmol), toluene (0.7 mL), RT. [b] Yields of isolated product. [c] Determined by HPLC methods.

(Table 4, entries 1–5). Similarly, the less studied and difficult 1-hexyne (**1c**) was reacted successfully with various *N*-tosyl imines to give the corresponding products in slightly lower enantiomeric excesses; however a few examples had *ee* values greater than 90% (Table 4, entries 5–10).

The absolute stereochemistry of compound **3aa** was determined to be *S* by chemical correlation[22] with (*S*)-(+)-*N*-tosylphenylglycine methyl ester (Scheme 2). The stereochemistry of the rest of the propargylic tosylamides (**3**) was assigned by analogy.



Scheme 2. Determination of the absolute stereochemistry of compound **3aa**. Ts = tosyl.



Scheme 3. Deprotection of the N-tosyl-protected amines (**3**).

The deprotection of the amino group in compounds **3ba** (63% *ee*) and **3ca** (81% *ee*), derived from 4-phenyl-1-butyne and 1-hexyne, respectively, was achieved by reduction with SmI_2[24] to provide corresponding propargylic amines **4ba** and **4ca** with acceptable yields and without any appreciable loss of optical purities (Scheme 3). Unfortunately, the presence of the phenyl group that is conjugated with the triple bond in compound **3aa**, derived from phenylacetylene, prevented all attempts to remove the tosyl group by reductive methods. Thus, treatment of **3aa** with SmI_2, or activation of the sulfonamide by acylation and subsequent reduction with Mg[25] promarily yielded 1,3-diphenylpropan-1-one, whereas direct reduction of **3aa** with Na/NH_3[26] gave 1,3-diphenylpropane as the major product. Other hydrolytic procedures gave unreacted starting material or complex mixtures.[27] Nevertheless, after quantitative hydrogenation of the triple bond in **3aa** (97% *ee*), the amino group of saturated tosyl amide **5aa** was deprotected with SmI_2, providing 1,3-diphenylpropan-1-amine (**6aa**) with good yield and without loss of enantiomeric excess (Scheme 3). Notably, this overall alkynylation/hydrogenation procedure is an alternative to the alkylation of *N*-tosyl imines with dialkylzinc reagents. This alternative is especially interesting since the enantioselective alkylation of imines with dialkylzinc reagents has been scarcely studied; most of the research has only been with small dialkylzinc reagents (i.e. Me_2Zn and Et_2Zn).[24b,28–30]

In conclusion, we have reported the first procedure for the catalytic enantioselective alkynylation of *N*-sulfonyl aldimines to give N-sulfonyl-protected propargylic amines by using dimethylzinc and binol-type ligands. Substitution of the binol ligand at the 3,3′ positions seems to be essential for obtaining high enantioselectivities. The reaction works with a variety of aromatic and heteroaromatic *N*-sulfonyl aldimines, and with different alkynes, providing the expected products with good yields (70–86%) and high enantiomeric excesses (76–100%). The *N*-tosyl amines derived from alkyl acetylenes can be efficiently transformed into the corresponding propargylic amines by treatment with SmI_2. Studies to extend the substrate scope and to clarify the mechanistic aspects of this reaction are underway and will be reported in due course.

Experimental Section

General experimental procedure for the enantioselective alkynylation: A 2 M solution of Me_2Zn in toluene (0.375 mL, 0.75 mmol) was added dropwise to pure alkyne **1** (0.9 mmol) at room temperature under argon. The reaction mixture was stirred for 1 h, after which a solution of ligand **L6** (17.7 mg, 0.025 mmol) in toluene (0.1 mL) was added by syringe. After 15 min, a solution of imine **2** (0.125 mmol) in toluene (0.225 mL) was added by syringe, and the reaction mixture was stirred until the reaction was complete (TLC). The reaction mixture was quenched with 1 M aqueous HCl (15 mL), extracted with

CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **3**.

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