Diastereoselective Synthesis of β-Substituted-α,γ-Diaminobutyric Acids and Pyrrolidines Containing Multichiral Centers

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Alkylzinc-Mediated Addition of Alkynes to *N*-Tosylaldimines: Enantioselective Synthesis of (*E*)-(2-En-3-ynyl)-amines

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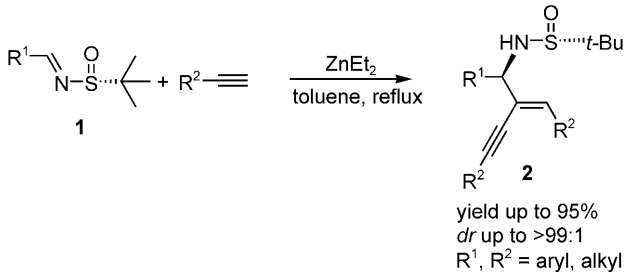
Abstract: An alkylzinc-mediated simple and efficient procedure for the catalytic enantioselective synthesis of *N*-tosyl-(*E*)-(2-en-3-ynyl)-amines has been developed. The method works well with various *N*-tosylaldimines and alkynes.

Keywords: alkynes; alkynylzinc reagents; asymmetric synthesis; *N*-tosylaldimines; propargylic amines

The development of new methods that lead to C–C bond formation by addition of nucleophiles to reactive functions, such as C=O and C=N double bonds, is fundamentally important in chemical synthesis.[1] In this field, the addition of an acetylenic reagent to carbonyl compounds or imines is one of the most important objectives, and the resulting propargylic alcohols or amines are versatile building blocks for the preparation of natural products, pharmaceuticals and plant protective agents.[2] Some excellent on promotion of the reactions of acetylenes with imines in high yields and enantioselectivities are known. In this context, the most reliable and efficient method for the preparation of propargylic amines is the addition of an appropriate alkynyl-metal to achiral imines or imines bearing chiral auxiliaries.[2b,3] The leading studies of this kind of reaction have been carried out by Carreira et al. using zinc-mediated alkyne additions.[4] Copper-catalyzed alkyne additions, disclosed by Li et al., also played a prominent role.[5] There have been a few examples of direct additions of alkynes to C=N electrophiles, in which an Ir,[6] Zr,[7] Ag[8] or Au[9] complex was used as a catalyst instead of a zinc or copper complex. Recently, Bolm's group has described the dimethylzinc-mediated addition of terminal alkynes to imines without any ligands,[4l] Pedro et al. reported a highly enantioselective zinc/BINOL-catalyzed alkynylation of *N*-sulfonylaldimines.[4m]

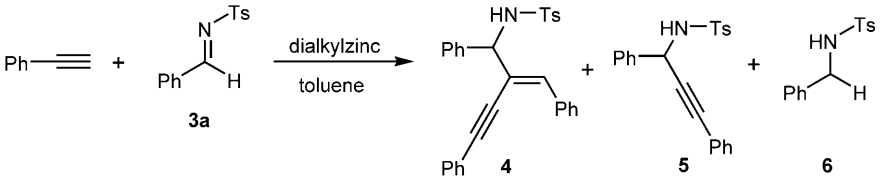
Recently, we have developed a novel method wherein chiral imines **1** were used to furnish *N*-*tert*-butylsulfinyl-(*E*)-(2-en-3-ynyl)-amines **2** with high yields and enantioselectivities (Scheme 1).[10] We hypothesized that, in this process, the nitrogen-zinc bond is very important, the zinc can coordinate with the alkyne and activate it to afford the π-complex which undergoes attack by another dialkynylzinc. Although this method failed to work with two different alkynes to afford diversified amines, it provided us with an opportunity to develop a highly efficient alkylzinc-mediated alkyne-imine addition. In this paper, the catalytic enantioselective synthesis of (*E*)-(2-en-3-ynyl)-amines has been carried out using BINOL-type ligands and *N*-tosylaldimines, and we found that the reaction of alkynes with *N*-tosylaldimine furnished *N*-tosyl-(*E*)-(2-en-3-ynyl)-amines in good yields and high enantiomeric excesses in the presence of dimethylzinc. Herein, we wish to report the results.



Scheme 1. Addition of alkynes to *N*-*tert*-butylsulfinylimines.

First, we examined the racemic synthesis of a 2-en-3-ynyl-amine. In an initial experiment, *N*-tosylbenzaldimine was added to a mixture phenylacetylene and diethylzinc under reflux to give a mixture of **4** and **6**

Table 1. Addition of phenylacetylene to *N*-tosylbenzaldimine. (Screening of reaction conditions).



Entry	Dialkylzinc (equiv.)	PhC≡CH (equiv.)	**4/5**[a]	**4/6**[a]	Yield of **4** [%]
1	$ZnEt_2$ (4)	4	–	3:1	60
2	$ZnEt_2$ (4)	8	–	5:1	72
3	$ZnMe_2$ (2)	2	1:4	–	19
4	$ZnMe_2$ (3)	3	4:1	–	79
5	$ZnMe_2$ (2)	4	>99:1	–	96
6[b]	$ZnMe_2$ (2)	4	<1:99	–	–
7[c]	$ZnMe_2$ (2)	4	<1:99	-	–

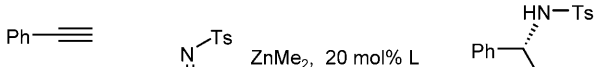
[a] The ratio was detemined by ^{1}H NMR (400 MHz).
[b] THF as solvent.
[c] Dioxane as solvent.

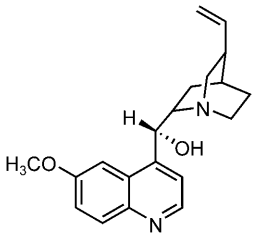
(Table 1, entries 1 and 2).[11] When $ZnMe_2$ was used instead of $ZnEt_2$, the 1,2-addition product **5** was found to be the major product (Table 1, entry 3). An excellent result was observed for the reaction with 2 equivalents of $ZnMe_2$ and 4 equivalents of alkyne, and the desired product **4a** was obtained in 96% yield (Table 1, entry 5). The solvent had a strong effect on this reaction. When the reaction was performed in THF or 1,4-dioxane, under the same conditions only the compound **5** was found (Table 1, entries 6 and 7).

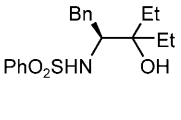
With these conditions in hand, we turned our attention to the enantioselective addition reaction and various ligands **L1**–**L5** were chosen. We found that the desired products were formed with low *ee* values by using **L1** (19% *ee*) and **L2** (25% *ee*). Then we changed to use BINOL-type ligands, which led to increased enantioselective excesses, and the best result was obtained when the ligand **L5** was used (87% yield and 93% *ee*) (Table 2).

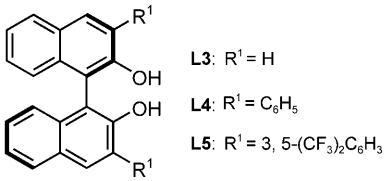
To test the general applicability, a series of functionalized *N*-tosylaldimines and alkynes were used. To be delighted, as shown in Table 3, the reaction works with a variety of aromatic and heteroaromatic *N*-tosylaldimines, and with different alkynes, providing the desired products with good yields (up to 92% yield) and high enantiomeric excesses (82–99% *ee*). The sterically hindered aldimines gave higher *ee* values, while benzaldimines bearing electron-rich groups resulted in decreased enantioselectivities. For example, *o*-methyl-substituted benzaldimine afforded a 99% *ee*, but *p*-methoxy-substituted benzaldimine gave 82% *ee* (Table 3, entries 3 and 8). It is more important that this method works with two different alkynes affording diversified amines (Table 3, entries 13–15).

Table 2. Enantioselective addition of phenylacetylene to *N*-tosylaldimine (**3a**). (Ligand optimization).[a]





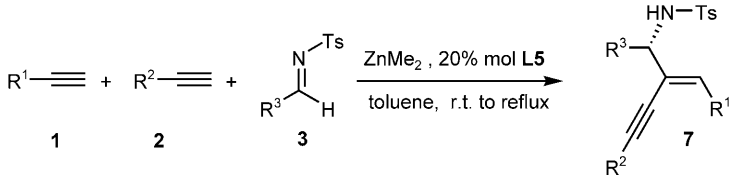




Entry	**L**	Yield [%][b]	*ee* [%][c]
1	**L1**	77	19
2	**L2**	84	−25
3	**L3**	88	38
4	**L4**	85	20
5	**L5**	87	93

[a] The reaction was performed with 1 mmol $ZnMe_2$ and 2 mmol alkyne.
[b] Isolated yields.
[c] Enantioselective excess was determined by HPLC.

Table 3. Enantioselective addition of alkynes to *N*-tosylaldimines. (Substrate scope of alkynes and aldimines).[a]

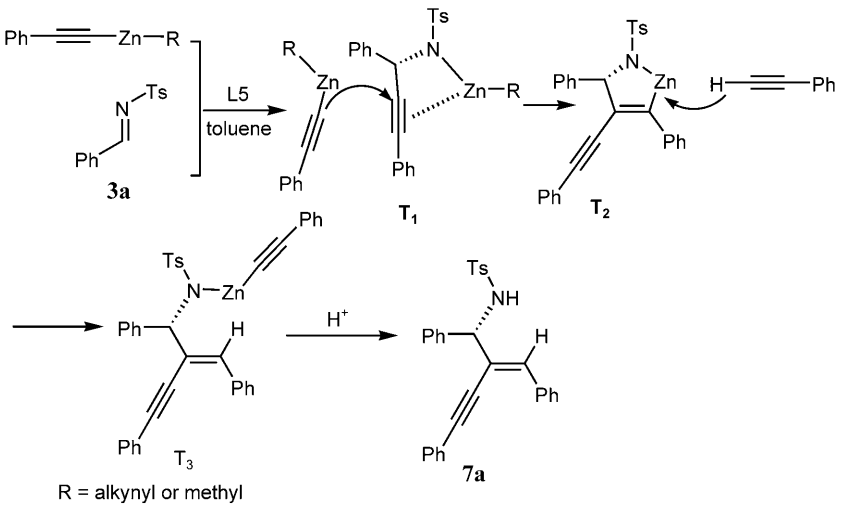


Entry	R^1	R^2	R^3	Product	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	Ph	**7a**	87	93
2	Ph	Ph	4-MeC_6H_4	**7b**	88	87
3	Ph	Ph	2-MeC_6H_4	**7c**	84	99
4	Ph	Ph	4-ClC_6H_4	**7d**	92	93
5	Ph	Ph	2-ClC_6H_4	**7e**	86	95
6	Ph	Ph	4-BrC_6H_4	**7f**	90	91
7	Ph	Ph	2-BrC_6H_4	**7g**	86	94
8	Ph	Ph	4-$MeOC_6H_4$	**7h**	82	82
9	Ph	Ph	2-FC_6H_4	**7i**	88	94
10	Ph	Ph	2-furyl	**7j**	73	84
11	*n*-C_5H_{11}	*n*-C_5H_{11}	Ph	**7k**	72	92
12	TMS	TMS	Ph	**7l**	51	85
13	Ph	*n*-C_5H_{11}	Ph	**7m**	64	92
14	*n*-C_5H_{11}	Ph	Ph	**7n**	57	94
15	Ph	4-$MeOC_6H_4$	Ph	**7o**	80	91

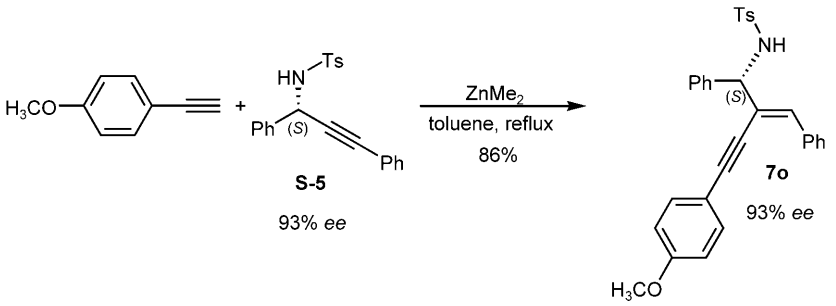
[a] See Supporting Information for details: entries 1–12 used Method A, entries 13–15 used Method B.
[b] Isolated yields.
[c] The *ee* values were determined by HPLC.

To study the mechanism, we carried out deuterium-labelling studies. When the reaction of **3a** with phenylacetylene was quenched with D_2O, the ratio of H to D of the double bond was 100:0. When the reaction was performed with deuterated phenylacetylene and **3a** then quenched with D_2O and H_2O, the ratios of H to D of the double bond were 3 to 97 and 4 to 96, respectively.

Our hypothesis is that alkynylzinc was formed *in situ* in analogy to the known chemistry of terminal alkyne and dimethyzinc. First, the 1,2-addition of alkynylzinc to **3a** afforded a π-complex intermediate $\mathbf{T_1}$,[2b,4m] which underwent an attack by another alkynylzinc to form a cyclic intermediate $\mathbf{T_2}$ under reflux conditions. The carbon-zinc bond could be cleaved by excess phenylacetylene to give the intermediate $\mathbf{T_3}$. Then, the reaction was quenched with HCl to give the product 7**a.** (Scheme 2) In support of this postulate, we used (*S*)-propargylamine **5** and 4-methoxyphenyl-



Scheme 2. Proposed mechanism.



Scheme 3. Mechanism study.

acetylene as the starting materials,[4m] the amine **7o** was obtained in 86% yield. (Scheme 3)

The *S* configuration of the product was determined by comparing its $[\alpha]_D$ value with the derivative described in the literature[10] (see Supporting Information).

In summary, we have developed a simple and efficient procedure for catalytic enantioselective synthesis of *N*-tosyl-(*E*)-(2-en-3-ynyl)-amines by the alkylzinc-mediated addition of alkynes to *N*-tosylaldimines in excellent *ee* values (82–99%). In particular, this method could be used to deal with two different alkynes to give diversified (*E*)-(2-en-3-ynyl)-amines successfully. The synthetic applications and the further mechanism study for this reaction are under investigation.

Experimental Section

General Experimental Procedure for the Enantioselective Addition of Alkynes to *N*-Tosylimines

Method A (Table 3, entries 1–12): Under nitrogen, toluene (2.0 mL), alkyne (2.0 mmol) and dimethylzinc (1.0 mmol, 1.0 mL) were charged in a Schlenk tube. After stirring for 2 h, a solution of ligand **L5** (71 mg, 0.1 mmol) in toluene was added. After stirring for 30 min, the *N*-tosylimine (0.5 mmol) was added and the solution was stirred until the reaction was complete (TLC). The reaction mixture was heated under reflux for 5 h. After being cooled to room temperature, the solution was quenched with 1 M aqueous HCl (5 mL), extracted with diethyl ether (3×20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compounds **7a–l.**

Method B (Table 3, entries 13–15): Under nitrogen, toluene (2.0 mL), alkyne **1** (0.55 mmol) and dimethylzinc (1.0 mmol, 1.0 mL) were charged in a Schlenk tube, After stirring for 2 h, a solution of ligand **L5** (71 mg, 0.1 mmol) in toluene was added. After being stirred for 30 min, the *N*-tosylimine (0.5 mmol) was added and the solution was stirred until the reaction was complete (TLC). Then alkyne **2** (2.0 mmol) was added and the reaction mixture was heated under reflux for 5 h. After being cooled to room temperature, the solution was quenched with 1 M aqueous HCl (5 mL), extracted with diethyl ether (3×20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compounds **7m–o.**

Acknowledgements

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