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# Enantioselective zinc-mediated conjugate alkynylation of saccharin-derived 1-*aza*-butadienes

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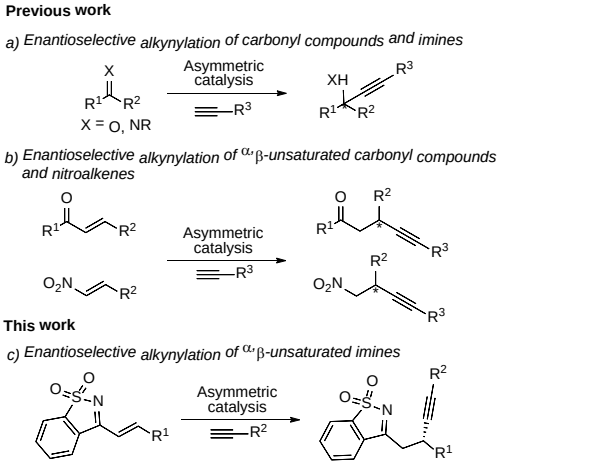
**The enantioselective 1,4-alkynylation of conjugated imines derived from saccharin with aryl- and alkyl- substituted terminal alkynes has been achieved. The reaction mediated by diethylzinc in the presence of a catalytic amount of a bis(hydroxy)malonamide chiral ligand provides the corresponding imines bearing a propargylic stereocenter with moderate yields and fair to excellent enantioselectivities.**

The C–C triple bond is present in the structures of many natural products and other organic compounds of interest in biochemistry and material science.[1] Furthermore, alkynes are versatile building blocks in synthetic organic chemistry that can undergo a broad range of transformation providing access to different functional groups and structural motifs.[2] Accordingly, the development of procedures to introduce a C–C triple bond in organic molecules is an important goal for many synthetic chemists. Among the different methodologies developed, those that exploit the acidic character of terminal alkynes are especially appealing. Thus, deprotonation of terminal alkynes with stoichiometric or catalytic amounts of base (in the presence of metal catalyst) provides nucleophilic metal alkynylides, which can react with carbon-based electrophiles to give internal alkynes with concomitant formation of a new C–C bond and, sometimes, of a new propargylic stereogenic center. In this context, considerable efforts have been devoted to the enantioselective alkynylation of carbonyl compounds[3] and imines[4] to give propargylic alcohols and amines, respectively (Scheme 1a). On the other hand, the enantioselective alkynylation of electrophilic C–C double bonds conjugated with electron-withdrawing groups has constituted a bigger challenge due to their lower electrophilicity and regioselectivity issues.[5] Nevertheless, considerable success has been obtained in the enantioselective alkynylation of conjugated carbonyl compounds[6] and nitroalkenes[7] under a variety of metal catalysis (Scheme 1b). However, despite these advances some limitations still remain. For instance, most of the reported procedures are appropriate for aryl- or trialkylsilyl- acetylenes but provide low enantioselectivities with alkyl-substituted alkynes.[5] Furthermore, developing conditions for the regio- and enantioselective alkynylation of other 1,4-acceptors, besides conjugated carbonyls and nitroalkenes, would be highly desirable.

Recently, α,β-unsaturated imines (1-*aza*-butadienes), the nitrogen analogues of enones, have been explored as Michael acceptors in enantioselective reactions.[8,9] However, although a synthesis of pyridines and pyrroles involving the copper-catalyzed conjugate addition of alkyl propiolates to *N*-sulfonyl *aza*-dienes has been reported,[10] there are no literature precedents on the enantioselective conjugate alkynylation of α,β-unsaturated imines to give chiral β-alkynyl imines bearing a propargylic stereocenter. Here, we describe our results on this elusive reaction (Scheme 1c), with special attention to the challenging aliphatic alkynes, affording chiral β-alkynyl imines




**Scheme 1** Enantioselective addition of terminal alkynes

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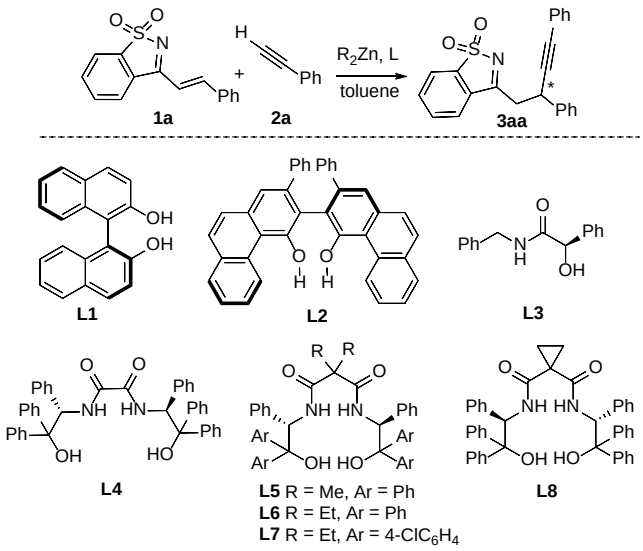
with excellent enantioselectivities.

Preliminary studies for the conjugate alkynylation of α,β-unsaturated imines were carried out using the addition of phenylacetylene to the *N*-tosylimine of chalcone mediated by zinc. However, although the applied conditions[11] led to the conjugate alkynylation product with fair levels of enantioselectivity, this was ineluctably obtained as an imine/enamine isomeric mixture (See SI). To avoid this drawback, saccharin-derived imines were chosen as substrates as we anticipated the preferential formation of the imine with the endocyclic double bond.[12] To begin with the optimization process, we studied the addition of phenylacetylene (**2a**) to saccharin-derived imine **1a** (Table 1).[11]

We initially tested the conditions developed in our group for the zinc-mediated conjugate alkynylation of unsaturated carbonyl compounds.[11] Under the initial conditions, the reactive system was prepared by heating a solution of ligand (20 mol%), alkyne **2a** (7.5 equiv.) and diethylzinc (2 equiv.) in toluene to 70 °C for 1 hour followed by addition of the imine **1a** after cooling to room temperature. Dihydroxybiaryl (**L1**, **L2**), mandelamide (**L3**), bis(hydroxy)oxamide (**L4**) and several bis(hydroxy)malonamide derivatives (**L5**-**L8**) were tested as chiral ligands. The most significative results are shown in Table 1 (see also SI). Ligands derived from 2,2-diethylmalonic acid and 1,1,2-triarylaminoethanol (**L6** and **L7**) provided the best results with similar performance for both ligands, compound **3aa** being obtained in ca 50% yield and 71% *ee* and 72% *ee*, respectively (Table 1, entries 6 and 7). Further optimization was performed with ligand **L7**. The effect of the catalyst load was examined. Increasing it to 30 mol% brought about a decrease of both yield and enantiomeric excess (Table 1, entry 9). On the other hand, only a slight decrease in the *ee* and yield was observed when the catalyst loading was reduced to 10 mol% (Table 1, entry 7 *vs* entry 10). Increasing the amount of diethylzinc from 2 to 4 equivalents in the presence of 10 mol% of **L7** allowed to improve the *ee* of the reaction up to 80% (Table 1, entry 11). Dimethylzinc was also tested but provided lower results than diethylzinc (Table 1, entry 12 *vs* 11). Finally, reducing the amount of alkyne **2a** to 5 equivalents increased the *ee* to 85%, while keeping the yield (Table 1, entry 13).

Under the best conditions available (Table 1, entry 13) we studied the scope of the enantioselective conjugate alkynylation of imines **1** (Table 2). First, we performed the addition of arylacetylenes to imines **1**. The results of the reaction were highly dependent on both the substituent on the β position of the double bond in compounds **1** and on the aryl group of the alkyne **2**. In most of the cases the addition products **3** were obtained with fair yields‡ and enantiomeric excesses (Table 2, entries 1-11). Interestingly, the addition of 4-phenyl-1-butyne (**2d**) to imine **1a** under the optimized conditions provided compound **3ad** with 90% *ee* together with some racemic ethylation product, which could be avoided by reducing

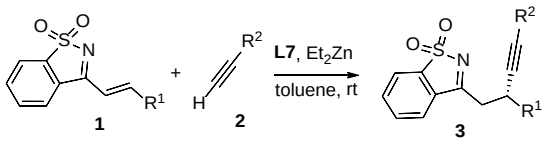
**Table 1** Optimization of reaction conditions.[a]




| Entry | L (mol%) | 2a (equiv.) | $Et_2Zn$ (equiv.) | t (h) | Yield (%) | *ee* (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **L1** (20) | 7.5 | 2 | 3 | 22 | 0 |
| 2 | **L2** (20) | 7.5 | 2 | 3 | 48 | -22 |
| 3 | **L3** (20) | 7.5 | 2 | 3 | 65 | 26 |
| 4 | **L4** (20) | 7.5 | 2 | 3 | 49 | 10 |
| 5 | **L5** (20) | 7.5 | 2 | 3 | 48 | -65 |
| 6 | **L6** (20) | 7.5 | 2 | 3 | 50 | -71 |
| 7 | **L7** (20) | 7.5 | 2 | 3 | 53 | -72 |
| 8 | **L8** (20) | 7.5 | 2 | 3 | 54 | 30 |
| 9 | **L7** (30) | 7.5 | 2 | 3 | 27 | -38 |
| 10 | **L7** (10) | 7.5 | 2 | 3 | 41 | -67 |
| 11 | **L7** (10) | 7.5 | 4 | 3 | 53 | -80 |
| 12[c] | **L7** (10) | 7.5 | 4 | 3 | 50 | -58 |
| 13 | **L7** (10) | 5 | 4 | 3 | 47 | -85 |

[a] **1a** (0.125 mmol), **2a**, 1.5 M $Et_2Zn$ in toluene, **L**, toluene (1.5 mL), rt. [b] Determined by HPLC with chiral stationary phases. Different sign indicates opposite enantiomers. [c] $Me_2Zn$ was used instead of $Et_2Zn$.

**Table 2** Conjugate addition of aryl-substituted terminal acetylenes **2** to unsaturated imines **1**.[a]



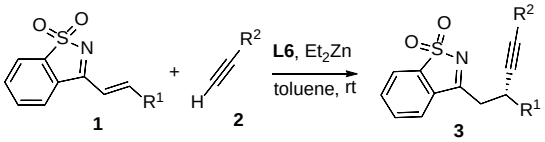

| Entry | 1 | $R^1$ | 2 | $R^2$ | 3 | Yield (%) | *ee* (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **a** | Ph | **a** | Ph | **3aa** | 47 | 85 |
| 2 | **b** | *p*-$BrC_6H_4$ | **a** | Ph | **3ba** | 59 | 69 |
| 3 | **c** | *p*-$MeOC_6H_4$ | **a** | Ph | **3ca** | 40 | 33 |
| 4 | **d** | *p*-$MeC_6H_4$ | **a** | Ph | **3da** | 33 | 58 |
| 5 | **e** | *o*-$MeC_6H_4$ | **a** | Ph | **3ea** | 36 | 53 |
| 6 | **f** | *m*-$MeC_6H_4$ | **a** | Ph | **3fa** | 35 | 71 |
| 7 | **g** | 2-naphthyl | **a** | Ph | **3ga** | 35 | 83 |
| 8 | **h** | 2-thienyl | **a** | Ph | **3ha** | 49 | 70 |
| 9 | **i** | *tert*-butyl | **a** | Ph | **3ia** | 84 | 35 |
| 10 | **a** | Ph | **b** | *p*-$ClC_6H_4$ | **3ab** | 43 | 83 |
| 11 | **a** | Ph | **c** | *p*-$MeOC_6H_4$ | **3ac** | 46 | 54 |
| 12[c] | **a** | Ph | **d** | $PhCH_2CH_2$ | **3ad** | 50 | 90 |

[a] **1** (0.125 mmol), **2** (0.625 mmol), 1.5 M $Et_2Zn$ in toluene (0.50 mmol), **L7** (0.025 mmol), toluene (1.5 mL), rt, 3 h. [b] Determined by HPLC with chiral stationary phases. [c] $Et_2Zn$ (0.25 mmol)

the amount of $Et_2Zn$ to 2 equivalents (Table 2, entry 12). This is a remarkable result, since historically alkyl acetylenes tend to give lower enantioselectivities than aryl acetylenes.[5] In the view of these promising results, we decided to further investigate the addition of alkyl-substituted terminal acetylenes. The performance of ligands **L6** and **L7** was re-evaluated in the addition of 4-phenyl-1-butyne (**2d**) to imine **1a**. In this case **L6** gave better result, allowing to obtain compound **3ad** in 68% yield and 95% *ee* (Table 2, entry 12 *vs* Table 3, entry 1). With **L6**, we studied the addition of a number of alkyl-substituted terminal acetylenes to several imines (Table 3).

Besides 4-phenyl-1-butyne (**2d**), the reaction could be carried out with other alkynes bearing a fully alkyl chain such as 1-hexyne (**2e**), the functionalized 6-chloro-1-hexyne (**2f**), the challenging cyclopropylacetylene (**2g**), as well as other functionalized alkynes bearing ester, benzyl ether or aryl ether groups (**2h**-**j**). Regarding the conjugated imine partner, the aryl group attached to the β-carbon of the double bond was amenable to variation, allowing the presence of electron-withdrawing or electron-donating groups at either the *ortho*-, *metha*- or *para*-positions of the phenyl ring. In all the cases, the alkynylated imines were obtained with excellent enantioselectivities (82-97% *ee*), especially when a *para*-substituted aryl group was used (Table 3).

**Table 3** Conjugate addition of alkyl-substituted terminal acetylenes **2** to unsaturated imines **1**.[a]




1 2 3

| Entry | 1 | $R^1$ | 2 | $R^2$ | 3 | Yield (%) | *ee* (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **a** | Ph | **d** | $PhCH_2CH_2$ | **3ad** | 68 | 95 |
| 2 | **b** | *p*-$BrC_6H_4$ | **d** | $PhCH_2CH_2$ | **3bd** | 35 | 96 |
| 3 | **a** | Ph | **e** | butyl | **3ae** | 44 | 88 |
| 4 | **b** | *p*-$BrC_6H_4$ | **e** | butyl | **3be** | 38 | 97 |
| 5 | **d** | *p*-$MeC_6H_4$ | **e** | butyl | **3de** | 42 | 92 |
| 6 | **a** | Ph | **f** | $Cl(CH_2)_4$ | **3af** | 48 | 96 |
| 7 | **b** | *p*-$BrC_6H_4$ | **f** | $Cl(CH_2)_4$ | **3bf** | 36 | 93 |
| 8 | **d** | *p*-$MeC_6H_4$ | **f** | $Cl(CH_2)_4$ | **3df** | 58 | 91 |
| 9 | **a** | Ph | **g** | cyclopropyl | **3ag** | 61 | 93 |
| 10 | **b** | *p*-$BrC_6H_4$ | **g** | cyclopropyl | **3bg** | 45 | 96 |
| 11 | **c** | *p*-$MeOC_6H_4$ | **g** | cyclopropyl | **3cg** | 69 | 93 |
| 12 | **d** | *p*-$MeC_6H_4$ | **g** | cyclopropyl | **3dg** | 69 | 93 |
| 13 | **e** | *o*-$MeC_6H_4$ | **g** | cyclopropyl | **3eg** | 55 | 85 |
| 14 | **f** | *m*-$MeC_6H_4$ | **g** | cyclopropyl | **3fg** | 64 | 82 |
| 15 | **a** | Ph | **h** | $PhCO_2CH_2$ | **3ah** | 63 | 93 |
| 16 | **a** | Ph | **i** | *p*-$MeOC_6H_4O(CH_2)_4$ | **3ai** | 66 | 99 |
| 17 | **a** | Ph | **j** | $PhCH_2OCH_2$ | **3aj** | 59 | 80 |
| 18[c] | **a** | Ph | **d** | $PHCH_2CH_2$ | **3ad** | 56 | 88 |

[a] **1** (0.125 mmol), **2** (0.625 mmol), 1.5 M $Et_2Zn$ in toluene (0.17 mL, 0.25 mmol), **L6** (0.0125 mmol), toluene (1.5 mL), rt, 3 h. [b] Determined by HPLC with chiral stationary phases. [c] Reaction carried out with 1.25 mmol of **1a**.

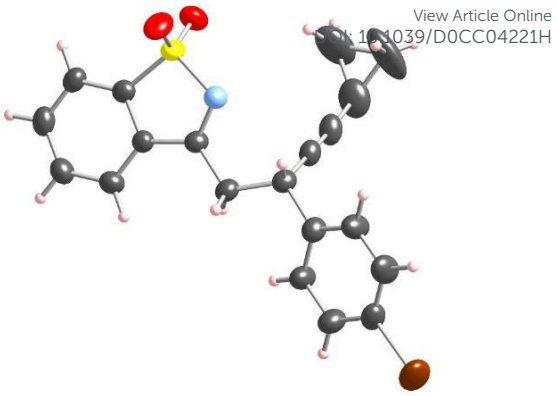
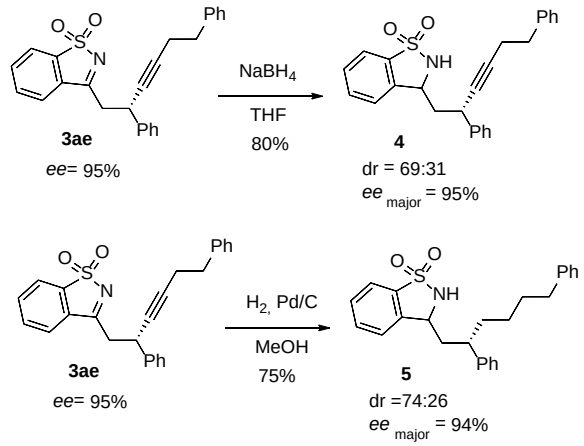


**Figure 1** Ortep plot for the X-ray structure of compound **3bg**. The thermal ellipsoids are drawn at the 50% probability level. Flack parameter 0.017(6).

The conjugate alkynylation of **1a** with 4-phenyl-1-butyne (**2d**) was scaled up to 1.25 mmol of **1a** providing the expected product **3ad** with good yield and some erosion of enantioselectivity, but still with high 88% *ee* (Table 3, entry 18). Compound **3bg** (Table 3, entry 10) could be crystallized and subjected to X-ray analysis, what allowed to establish the configuration of the stereogenic center as *S* (Figure 1).§ The absolute stereochemistry of all compounds **3** was assigned by analogy upon the assumption of a uniform stereochemical pathway.

Scheme 2 shows some transformations on compound **3ae** that show the potential application of compounds **3** in the synthesis of optically active benzosultams. Thus, selective reduction of the imine could be achieved by treatment with sodium borohydride in THF to give alkyne **4** in 80% yield as a 69:31 mixture of two diastereomers without erosion of the enantiomeric excess. On the other hand, compound **5** was obtained in 75% yield, as a 74:26 diastereomer mixture without loss of enantiomeric excess, after simultaneous reduction of the triple bond and the imine by catalytic hydrogenation on 10% Pd/C.




**Scheme 2** Synthetic transformations of compound **3ae**.

In summary, we have reported the first example of enantioselective conjugate alkynylation of α.β-unsaturated

imines (1-*aza*-butadienes). A reactive system formed by a terminal alkyne, diethylzinc and a chiral bis(hydroxy)malonamide allowed the enantioselective alkynylation of C–C double bonds conjugated with saccharin-derived imines to give the corresponding alkynylated imines bearing a propargylic stereocenter. The reaction can be performed with terminal alkynes of different characteristics and, remarkably, it is most convenient for alkyl-substituted alkynes. The results anticipated the potential application of this catalytic system to other unsaturated imines sucha as chalcone imines. Research with this regard is underway in our laboratory.

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## Conflicts of interest

There are no conflicts to declare

## Notes and references

‡ In some cases we observed the formation of the conjugate ethylation product in some extent. This fact together with the low solubility showed by some of the products may account in part for the obtained fair yields. The mass balance in three representative entries (Table 2, entry 1 and Table 3, entries 16 and 17) can be found in the SI.

§ CCDC-1992564 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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