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Enantioselective Synthesis of 4-Substituted Dihydrocoumarins through a Zinc Bis(hydroxyamide)-Catalyzed Conjugate Addition of Terminal Alkynes

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Abstract: A new enantioselective catalyst for the conjugate addition of terminal alkynes has been developed. Terminal alkynes react with 3-alkoxycarbonylcoumarins in the presence of diethylzinc and bis(hydroxyamide) ligands to give chiral non-racemic dihydrocoumarins substituted with an alkynyl group on the C-4 position with good yields and enantiomeric excesses up to 95%.

Keywords: alkynylation; asymmetric catalysis; N,O ligands; nucleophilic addition; oxygen heterocycles

The 3,4-dihydrocoumarin ring system constitutes the core of many natural products[1] and biologically active compounds. Over the past decades, numerous dihydrocoumarin derivatives and related compounds have been discovered or obtained synthetically, which exhibited estrogen-like,[2] protein transacetylase,[3] reductase inhibitory,[4] protein kinase,[5] antiherpetic,[6] cytotoxic,[7] antioxidant and antiproliferative,[8] or blocking of ATP-sensitive potassium channels activities,[9] among others. Natural dihydrocoumarins are also of great interest as flavouring agents in the food industry.[10] Furthermore, dihydrocoumarins have been used as building blocks for the synthesis of other bioactive compounds.[11] For these reasons, the development of new synthetic procedures for the construction or modification of this scaffold has attracted considerable attention among chemists. The conjugate addition of carbon nucleophiles to coumarins is one of most straightforward methods for the synthesis of 3,4-dihydrocoumarins bearing a substituted stereogenic center at the 4-position of the heterocycle.

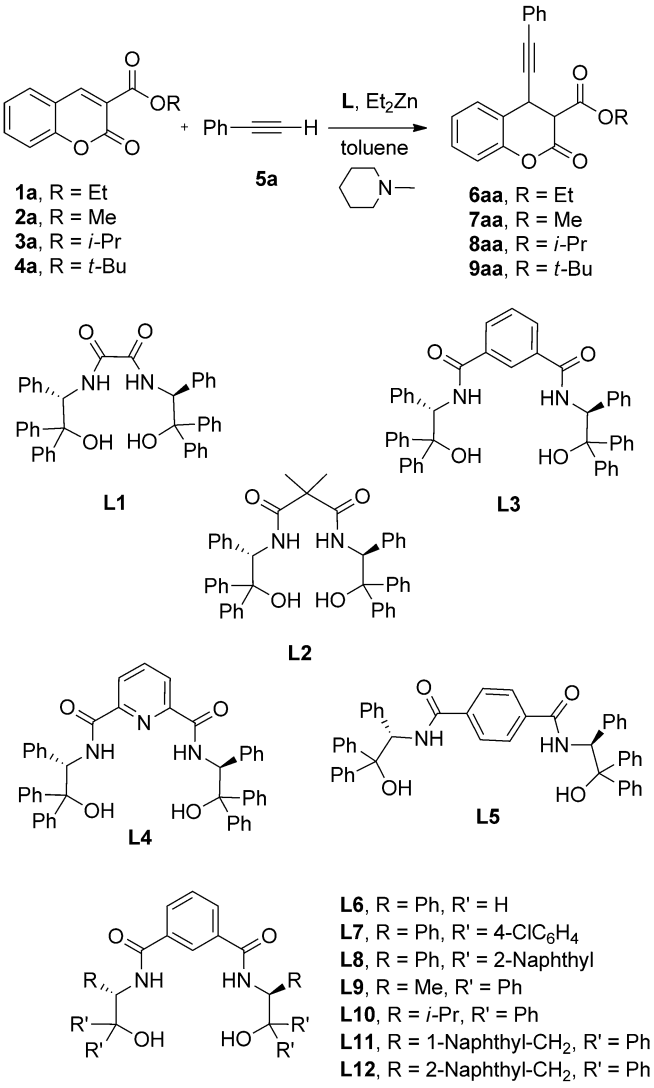
The enantioselective conjugate addition of arylboronic acids to coumarins employing chiral Rh complexes has been reported by Hayashi[12] and Carreira.[13] The Cu-catalyzed conjugate addition of dialkylzinc reagents to 3-acyl- and 3-nitrocoumarins using phosphoramidite ligands has been described by Woodward[14] and Feringa,[15] respectively. This latter author has reported recently the asymmetric addition of Grignard reagents catalyzed by copper.[16] Finally, Feng has developed a catalytic asymmetric conjugate allylation of 3-acylcoumarins with tetraallyltin *via* a dual activation strategy using *N*,*N*-dioxide-Yb(OTf)$_3$ and (CuOTf)$_2$·C$_7$H$_8$.[17] However, an asymmetric conjugate alkynylation of coumarins has never been achieved, to the best of our knowledge.

The asymmetric conjugate alkynylation of unsaturated ketones has been carried out by using BINOL-derived chiral alkynylboronates[18] or alkynylalanes in the presence of a nickel catalyst.[19] Hayashi and Nishimura have described the conjugate alkynylation of enones with silylacetylenes catalyzed by either rhodium[20] or cobalt complexes.[21] Recently, our group has also developed an asymmetric conjugate alkynylation of enones mediated by Et$_2$Zn and VANOL.[22] On the other hand the conjugate alkynylation of unsaturated esters has been only possible with double-activated substrates such as 5-alkylidene-Meldrum acid derivatives. Thus, Carreira[23] and Fillion[24] have reported separately the conjugate addition of terminal alkynes to these substrates catalyzed by copper or rhodium, respectively, whilst Cui and Walker have used alkynyl-Grignard reagents in the presence of a chiral amino alcohol for this purpose.[25] Herein, we describe the asymmetric alkynylation of 3-alkoxycarbonylcoumarins using a new Zn-bis(hydroxyamide) catalyst. To the best of our knowledge, this is the first reported example of the alkynylation of coumarins, but also the first example of a zinc-mediated alkynylation of unsaturated esters that requires substoichiometric amounts of chiral inducer.

At the onset of our investigation we studied the reaction between 3-ethoxycarbonylcoumarin (**1a**) and phenylacetylene (**5a**) to give compound **6aa** (Scheme 1) under identical conditions to those used previously by us for the conjugate alknylation of enones (Et_2Zn-binaphthol ligands).[22] However, with this system the alkynylation product **6aa** was obtained in racemic form with low yield, together with the 4-ethyl derivative. Then, we screened the use of bis(hydroxyamide) ligands **L1** and **L2** that we had successfully used in the past for the enantioselective diethylzinc addition to aldehydes (Table 1, entries 1 and 2).[26] Although **L1** led to the expected product in racemic form, the encouraging result obtained with ligand **L2** prompted us to synthesize and test other C_2-symmetrical bis-hydroxyamides **L3**–**L12**.

In general, bis(hydroxyamide) **L3** derived from 2-amino-1,1,2-triphenylethanol and isophthalic acid gave better results than amides derived from the same amino alcohol and other acid scaffolds (entries 1–5). The presence of diarylmethanol units in the ligand was essential to obtain enantioselectivity (entry 6 *vs.* entries 5, 7–12), the best result being obtained when R′ = Ph (entry 3 *vs.* entries 7, 8). Finally, the highest yield and enantioselectivity were obtained with ligands **L3** and **L11** (entries 3 and 11).

Next we continued the optimization process with **L11** and studied the effect of the 3-alkoxycarbonyl group (Table 2). With the bulkier 3-*tert*-butoxycarbon-



Scheme 1. Conjugate addition of phenylacetylene to 3-alkoxycarbonylcoumarins and ligands used in this study.

Table 1. Conjugate addition of phenylacetylene (**5a**) to 3-ethoxycarbonylcoumarin (**1a**) according to Scheme 1. Screening of ligands.[a]

Entry	L	*t* [h]	Yield [%][b]	*ee* [%][c]
1	L1	4	34	0
2	L2	2	73	50
3	L3	2	78	67
4	L4	5	63	10
5	L5	2	66	40
6	L6	4	55	0
7	L7	1	76	47
8	L8	2	79	34
9	L9	1	86	37
10	L10	1	61	20
11	L11	1	80	68
12	L12	1	72	55

[a] **1a** (0.125 mmol), **5a** (0.9 mmol), **L** (0.025 mmol), Et_2Zn (0.25 mmol), *N*-Me-piperidine (0.05 mmol).
[b] Isolated yield of **6aa**.
[c] Determined by HPLC.

Table 2. Conjugate addition of phenylacetylene (**5a**) to 3-alkoxycarbonylcoumarins (**1a–4a**) according to Scheme 1.[a]

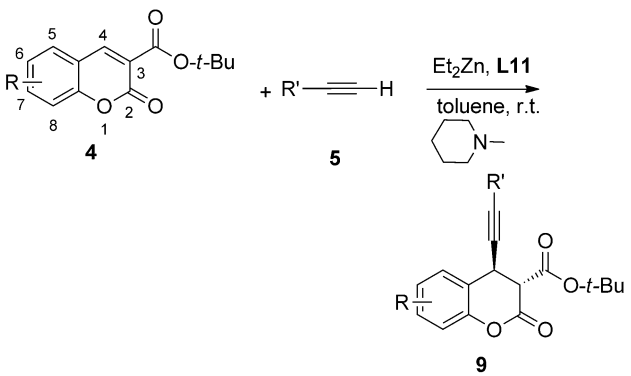
Entry		R	Co-solvent	*T* [°C]		Yield [%][b]	*ee* [%][c]
1	1a	Et		r.t.	6aa	65	68
2	2a	Me		r.t.	7aa	80	58
3	3a	*i*-Pr		r.t.	8aa	75	65
4	4a	*t*-Bu		r.t.	9aa	82	72
5[d]	4a	*t*-Bu		r.t.	9aa	69	68
6	4a	*t*-Bu	hexane	r.t.	9aa	87	66
7	4a	*t*-Bu	CH_2Cl_2	r.t.	9aa	99	64
9	4a	*t*-Bu	toluene	40	9aa	83	54
10	4a	*t*-Bu		0	9aa	60	72
11[e]	4a	*t*-Bu		r.t.	9aa	60	72
12[f]	4a	*t*-Bu		r.t.	9aa	58	65

[a] **1a–4a** (0.125 mmol), **5a** (0.9 mmol), **L11** (0.025 mmol), Et_2Zn (0.25 mmol), *N*-Me-piperidine (0.05 mmol).
[b] Isolated yield.
[c] Determined by HPLC.
[d] Me_2Zn was used instead of Et_2Zn.
[e] 10 mol% of **L11** was used.
[f] 5 mol% of **L11** was used.

yl derivative **4a** we observed an increase in both yield and enantioselectivity with respect to other alkoxy groups, compound **9aa** being obtained with 82% yield and 72% *ee* (entry 4). The use of Me_2Zn instead of Et_2Zn, as well as the use of other co-solvents or reaction temperatures did not bring about any improvement (entries 5–10). We also tested the effect of the catalyst load. The reaction could be carried out in the presence of only 10 mol% of ligand **L11** without any effect on the enantioselectivity (entry 11), although compound **9aa** was obtained with lower yield (60%). A further decrease of the catalytic load to 5 mol% (entry 12) brought about a decrease of both enantioselectivity and yield with respect to 20 mol% catalyst load.

Despite the fair results attained in the test reaction with ligand **L11** (Table 2, entry 4, footnote [a]),[27] we were encouraged to continue with the study of the scope of the reaction under the best reaction conditions. A number of substituted 3-*tert*-butoxycarbonylcoumarins **9a–j** were synthesized and reacted with phenylacetylene **5a** (Scheme 2, Table 3, entries 1–10). The presence of substituents with either electron-donating or electron-withdrawing nature on the aromatic ring of the coumarin favoured higher enantioselectivities with respect to the unsubstituted coumarin. The highest enantioselectivities were obtained with coumarins substituted on the C-7 or C-8 positions (entries 2, 3 *vs.* entries 4, 5). In particular, excellent enantioselectivities (*ee* above 90%) were obtained with coumarins bearing an alkyl group (Me or *t*-Bu) at the C-8 position (entries 6, 7).[28] We also tested some disubstituted coumarins. Again, excellent results were obtained with coumarins bearing an alkyl group on C-8 (entries 9, 10).

Next, we tested the use of other terminal alkynes. Aliphatic alkynes such as 4-phenyl-1-butyne (**5b**) were tolerated, although the addition product was obtained with lower yield and enantiomeric excess (entries 11, 12). Ethyl propiolate (**5f**) did not react with **4a** under the optimized conditions, the starting material being recovered unaltered (entry17). The reaction



Scheme 2. Conjugate addition of alkynes to coumarins.

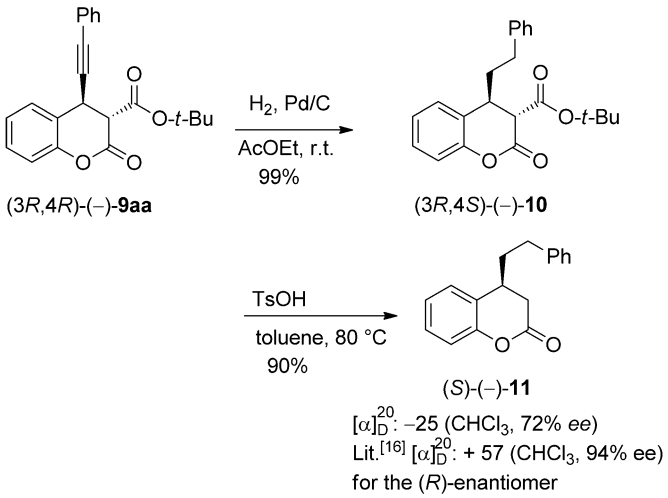
Table 3. Conjugate addition of alkynes **5** to 4-*tert*-butoxycarbonylcoumarins **4** according to Scheme 2.[a]

Entry	4	R	5	R′	9	Yield [%][b]	*ee* [%][c]
1	a	H	a	Ph	9aa	82	72
2	b	5-MeO	a	Ph	9ba	76	76
3	c	6-MeO	a	Ph	9ca	70	75
4	d	7-MeO	a	Ph	9da	80	85
5	e	8-MeO	a	Ph	9ea	70	84
6	f	8-Me	a	Ph	9fa	97	91
7	g	8-*t*-Bu	a	Ph	9ga	85	95
8	h	6-Br	a	Ph	9ha	78	80
9	i	6,8-(*t*-Bu)$_2$	a	Ph	9ia	82	89
10	j	6-Cl, 8-Me	a	Ph	9ja	85	93
11	a	H	b	Ph(CH$_2$)$_2$	9ab	36	60
12[d]	a	H	b	Ph(CH$_2$)$_2$	9ab	40	66
13	f	8-Me	c	3-FC$_6$H$_4$	9fc	92	87
14	f	8-Me	d	4-MeOC$_6$H$_4$	9fd	99	81
15	j	6-Cl, 8-Me	c	3-FC$_6$H$_4$	9jc	77	92
16	j	6-Cl, 8-Me	e	4-FC$_6$H$_4$	9je	73	92
17	a	H	f	CO$_2$Me	–	NR[e]	–
18	f	8-Me	g	Me$_3$Si	–	95[f]	–

[a] **4** (0.125 mmol), **5** (0.9 mmol), **L11** (0.025 mmol), Et_2Zn (0.25 mmol), *N*-Me-piperidine (0.05 mmol).
[b] Isolated yield.
[c] Determined by HPLC.
[d] Ligand **L3** was used.
[e] Compound **4a** was recovered unreacted.
[f] Product of ethyl 1,4-addition.

of trimethylsilylacetylene (**5g**) with alkoxycarbonylcoumarin **4f** was also tested. However, under the optimized conditions, we only observed conjugate addition of the ethyl group instead of alkynylation (entry 18). Prolongation of the reaction time between **5g** and diethylzinc from 1.5 h to 3 h prior to addition of the substrate **4f** gave a non-reactive species and compound **4f** was recovered unaltered under these conditions. Other substituted arylacetylenes reacted with a number of coumarins with excellent yields and high enantioselectivities. In particular, (3-fluorophenyl)ethyne (**5c**) and (4-fluorophenyl)ethyne (**5e**) reacted with disubstituted coumarin **4j** to give the expected products **9jc** and **9je** with 92% *ee* in both cases (entries 15 and 16).

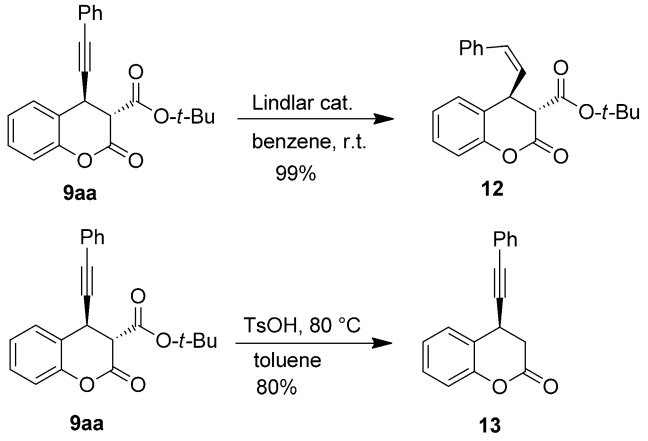
In all the cases products **9** were obtained as a single diastereomer that was identified as that having the *trans* disposition between the *tert*-butoxycarbonyl and alkynyl groups as it was shown by X-ray analysis of compound **9ha**.[29] Unfortunately, these crystals were not suitable for a determination of the absolute stereochemistry. Nevertheless, we were able to determine the absolute stereochemistry of compound **9aa** by chemical correlation with compound **11** of known stereochemistry (Scheme 3). A sample of compound **9aa** (72% *ee*) was hydrogenated over Pd/C to give compound **10** with quantitative yield, which after hy-



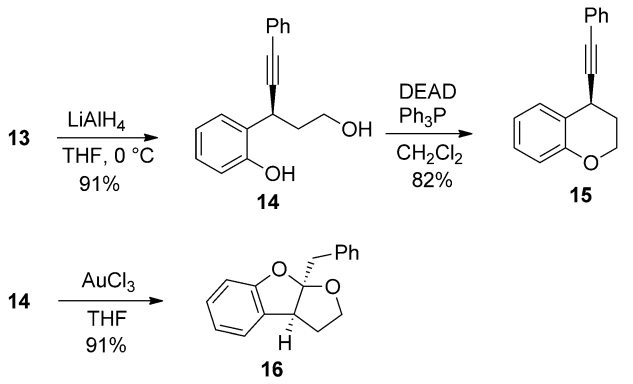
Scheme 3. Determination of the absolute stereochemistry of compound **9aa**.

drolysis and decarboxylation gave 3-(2-phenylethyl)-dihydrocoumarin **11**. By comparison of the optical rotation sign and chiral chromatography retention times of compound **11** obtained in this way with those described in the literature for the (*R*)-enantiomer of compound **11**,[16] we could establish that our prepared compounds **10** and **11** should be of *S* configuration at C-4 and compound **9aa** should have the *R* configuration at this stereogenic center.[30] For the rest of compounds **9**, the stereochemistry was assigned upon the assumption of a common stereochemical mechanism.

The triple bond in compound **9aa** can also be partially hydrogenated with Lindlar catalyst to give the alkenylated coumarin **12** having a *Z*-double bond in quantitative yield without detriment on the optical purity (Scheme 4). On the other hand, the *tert*-butoxycarbonyl group at C-3 can be removed by selective hydrolysis-decarboxylation after treatment with



Scheme 4. Partial hydrogenation of the triple bond and decarboxylation of compound **9aa**. All the reactions took place without lost of optical purity.



Scheme 5. Synthetic transformations from dihydrocoumarin **13**. All the reactions took place without lost of optical purity.

TsOH in toluene to give 4-alkynylated coumarin **13.** Therefore, the alkoxycarbonyl group on C-3 can be considered as an auxiliary that increases the reactivity of the double bond, which can be later removed from the molecule.[31]

Alkynylcoumarin **13** can be reduced upon treatment with $LiAlH_4$ to give alcohol **14** (Scheme 5), which after Mitsunobu reaction yields the chromane **15**, which is the starting material for the synthesis of other 4-(phenylethynyl)chromanes with antihypertensive activity.[32] On the other hand, gold-catalyzed cyclization of diol **14** leads to *cis*-fused acetal **16** having the tetrahydrofuro[2,3-*b*]benzofuran skeleton characteristic of fungal metabolite aflatoxins[33] and other natural products.[34]

In summary, we have developed a procedure for the enantioselective synthesis of 4-substituted dihydrocoumarins *via* the enantioselective alkynylation of 3-alkoxycarbonylcoumarins. The reaction is carried out by a novel catalytic system that uses C_2-symmetrical bis-hydroxyamides, diethylzinc and terminal alkynes. The alkynylated products are obtained with good yields and with enantiomeric excesses between 60 and 94%, depending on the substitution of both the alkyne and the coumarin. Although most of the study has been carried with 20 mol% catalyst loading, this can be reduced to 10 mol% without affecting the enantioselectivity of the reaction, although with a decrease of yield. The potential synthetic applicability of the resulting products has been shown by diverse transformations. Further studies to enlarge the scope of the reaction as well as new synthetic applications of the resulting products are underway.

Experimental Section

General Procedure for the Enantioselective Conjugate Alkynylation of Coumarins

A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of ligand **L11** (11.3 mg, 0.025 mmol) and alkyne **5** (0.94 mmol) in dry toluene (0.48 mL) at room temperature under nitrogen. The mixture was stirred at 70 °C for 1.5 h, during this time a white precipitate was formed. After cooling to room temperature, a solution of coumarin **4** (0.125 mmol) and *N*-methylpiperidine (6.1 μL, 0.05 mmol) in toluene (1.0 mL) was added *via* syringe and the solution was stirred until the reaction was complete (1–4 h, TLC). During this time the precipitate slowly dissolved. The reaction mixture was quenched with 20% aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2 × 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc mixtures afforded compound **9**.

Acknowledgements

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[27] The use of *N*-methylpiperidine is not essential for the reaction to proceed. We found identical enantioselec-

tivities with or without this base. However, the use of *N*-methylpiperidine provided better yields.

[28] A similar effect has been found by Fillion in the enantioselective 1,4-addition of dialkylzinc reagents to 5-(1-arylalkylidene)-Meldrum's acid derivatives, where the location and nature of the substituent on the aryl group determined the enantioselectivity of the reaction, see: a) E. Fillion, A. Wilsily, *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775; b) A. Wilsily, E. Fillion, *Org. Lett.* **2008**, *10*, 2801–2804; c) A. Wilsily, E. Fillion, *J. Org. Chem.* **2009**, *74*, 8583–8594.

[29] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 916051. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.:(+44)-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

[30] This change in the stereochemical notation is due to a change in the priority order of the substituents from **9aa** to **12** when applying the Cahn–Ingold–Prelog rules.

[31] The presence of the 3-alkoxycarbonyl moiety is mandatory. The reaction of phenylacetylene with unsubstituted coumarin does not take place under the optimized conditions.

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