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Mandelamide−Zinc-Catalyzed Enantioselective Alkyne Addition to Heteroaromatic Aldehydes[#]

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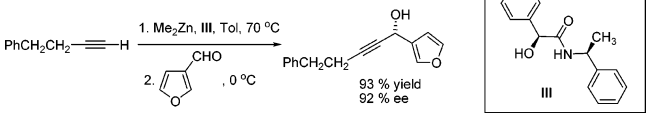

The (*S*,*S*)-mandelamide **III** catalyzes the additions of both aryl- and alkylalkynylzinc reagents to heteroaromatic aldehydes with good yields and enantioselectivities up to 92%. This catalyst is easily prepared in a one-step procedure, and both enantiomers are available. Unlike most other described methods, using this catalyst does not require the addition of $Ti(O^iPr)_4$.

The asymmetric addition of metalated terminal alkynes to aldehydes is one of the most important methods for producing chiral secondary propargylic alcohols because it forms a new C−C bond with concomitant creation of a stereogenic center in a single transformation. The resulting optically active propargylic alcohols are versatile building blocks for the synthesis of a wide range of natural products and pharmaceuticals, and besides, its acetylene and hydroxyl functions can be used to construct very diverse molecular structures. Among many organometallic nucleophiles, organozinc reagents tolerate the presence of many functional groups that are reactive toward organolithium and Grignard reagents. This property renders the organozinc species attractive useful alternatives to these highly active reagents.[1]

In their pioneering work, Carreira and co-workers discovered that zinc acetylides, generated in situ from the reaction of terminal alkynes and $Zn(OTf)_2$ in the presence of triethylamine, could enantioselectively add to aliphatic aldehydes when promoted by the chiral ligand *N*-methylephedrine, and a high enantiomeric excess up to 99% was achieved.[2] However, aromatic aldehydes cannot be used in this catalytic system due to Cannizzaro reaction.[2b] Chan and co-workers[3] have disclosed that a combination of chiral BINOL and sulfonamide with $Ti(O^iPr)_4$ generates a highly enantioselective catalyst which catalyzes the addition of alkynylzinc, produced in situ from the reaction of phenylacetylene and dimethylzinc, to aromatic aldehydes. Pu and co-workers developed a more convenient procedure, using the BINOL/$Ti(O^iPr)_4$/Et_2Zn combination, to produce highly optically active secondary propargylic alcohols, in which aliphatic and aromatic aldehydes are both suitable substrates.[4] Wang and co-workers recently found that complexes of sulfonamide alcohols and $Ti(O^iPr)_4$ also catalyze the highly enantioselective addition of phenylacetylene to both alkyl and aromatic aldehydes.[5] Other chiral ligands, including *Cinchona* alkaloids,[6] terpene- and carbohydrate-derived amino alcohols,[7] ferrocenyl oxazoline alcohols,[8] paracyclophane-based imine phenols,[9] oxazolidines,[10] N-substituted proline,[11] and β-hydroxy amides,[12] have also been reported to catalyze this asymmetric addition reaction. Very recent developments have been reported: Shibasaki and co-workers[13] have described a catalytic asymmetric alkynylation of aldehydes promoted by the In(III)/BINOL complex and Cy_2NMe, based in a dual activation of both substrates due to the "bifunctional character" of In(III), and Trost and co-workers[14] have reported a practical alkynylation of aromatic and α,β-unsaturated aldehydes using their proline-derived dinuclear zinc catalyst system, with high reactivity and enantioselectivity.

Despite the significant results achieved in this area, efforts to develop new types of efficient chiral catalysts for this

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[#] This work is dedicated to the memory of Professor Marcial Moreno-Mañas.

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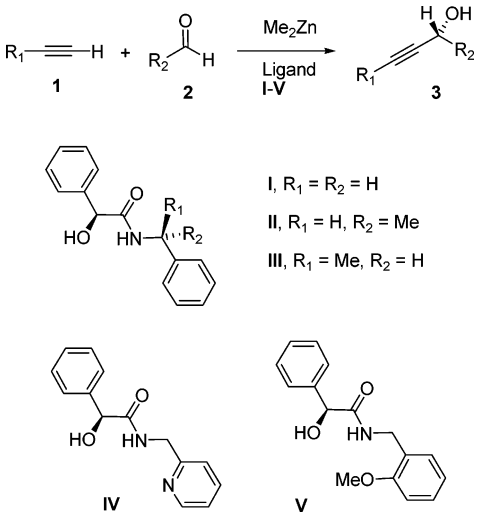
SCHEME 1. Alkynylation of Aldehydes in the Presence of Dimethylzinc and Mandelamides as Chiral Ligands



important asymmetric reaction are still in great need to probe the relation between the ligand structure and catalytic activity. Our group has been developing hydroxy amide chiral ligands that are synthesized conveniently in simple, short sequences and from cheap, available chiral resources.[15] Recently, we disclosed that simple (*S*)-mandelamides could be used to effectively catalyze the addition of dimethylzinc to α-ketoesters with good yield and enantioselectivity,[16] as well as, in combination with $Ti(O^iPr)_4$, to aromatic aldehydes with moderate to good enantioselectivity.[17] Herein, we wish to report the use of (*S*)-mandelamides as chiral ligands in the alkynylation of benzaldehyde and heteroaromatic aldehydes, particularly 2- and 3-furanecarbaldehyde and 2- and 3-thiophenecarbaldehyde, with several terminal alkynes (Scheme 1).

The reaction with these heteroaromatic aldehydes is particularly interesting because of the possibility of manipulation on the heterocyclic ring. Thus, 2-furyl alcohols can be transformed into 6-hydroxy-2*H*-pyran-3(6*H*)-ones, important building blocks for the synthesis of biologically active natural products, through an oxidative rearrangement (Figure 1).[18] On the other hand, the thiophene ring in the resulting thienyl alcohols can be desulfurized with Raney nickel acting as a masked four-carbon synthon.[19] However, despite the synthetic utility of these products, the alkynylation of furane- and thiophenecarbaldehydes has been little explored and remains an interesting challenging reaction.

To optimize the reaction conditions, we first studied the asymmetric reaction of phenylacetylene (**1a**) with benzaldehyde (**2a**). Initially, the reaction was carried out using 0.2 equiv of

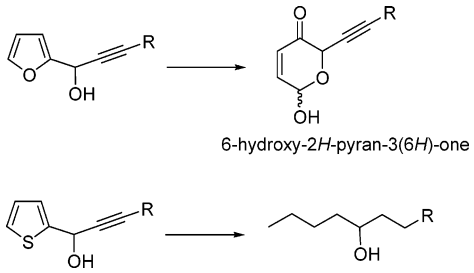


FIGURE 1. Modification of heteroaromatic propargylic alcohols.

mandelamide **I** ligand in combination with $Ti(O^iPr)_4$ (1.4 equiv), 2 M Me_2Zn in toluene (6 equiv), and phenylacetylene (7.2 equiv) in dichloromethane solution (5 mL) at 0 °C. These reaction conditions are very similar to those reported by Chan[3] and Pu[4a,b] for this same reaction using BINOL as chiral ligand. However, with mandelamide **I** as ligand, 1-phenylethanol, which results after methyl addition to benzaldehyde, was the main reaction product (55%), the desired propargylic alcohol **3aa** being obtained in only 40% yield (entry 1). Using toluene as the solvent and in absence of $Ti(O^iPr)_4$, the formation of the methyl addition product could be avoided and the propargylic alcohol **3aa** was obtained with moderate yield (65%) although with low enantioselectivity (51% ee) (entry 2).

The effect of the N-substituent of the ligand was studied with mandelamides **II**−**V**. Thus, ligands **II** and **III** introduce an additional stereogenic center on the amide substituent, while ligands **IV** and **V** introduce an additional potentially coordinating atom. In the presence of ligands **II**−**V**, the reaction took place with good yields but with variable enantioselectivity. Thus, ligands **I** and **III** gave the reaction product with similar enantiomeric excesses (51 and 50% ee, respectively, entries 2 and 4), ligands **II** and **V** lead to lower enantioselectivities (29 and 31% ee, respectively, entries 3 and 6), and the reaction yielded almost racemic product with ligand **IV** (entry 5). Some interesting results were obtained, however, when the reaction was carried out at higher temperatures: at 50 °C, the enantioselectivity observed with ligand **I** decreased to 42% ee, while with ligands **II** and **III**, it increased to 34 and 65% ee, respectively. A further increase of the temperature to 70 °C brought about a new decrease in the enantioselectivity with ligand **I** (40% ee) and a new enantiomeric excess increase with ligands **II** and **III** (48 and 70% ee, respectively).

To improve the enantioselectivity of the reaction, we decide to preform the alkynylzinc reagent prior to the addition of the aldehyde. According to the procedure described by Pu,[4a] phenylacetylene was treated with Me_2Zn at 70 °C for 30 min until the formation of a white precipitate in the reaction mixture appeared. The reaction temperature was lowered to 0 °C, and then mandelamide **III** was added followed by benzaldehyde (Scheme 2, eq 1). However, under these reaction conditions, the desired propargylic alcohol **3aa** was obtained in practically racemic form (3% ee, entry 13). This result indicated that the simultaneous presence of Me_2Zn and mandelamide **III** was essential for the formation of the catalyst.[20] Effectively, to obtain a good enantioselectivity, it was necessary to heat at 70 °C phenylacetylene with dimethylzinc in toluene in the presence of mandelamide **III** and then to add benzaldehyde at 0 °C (entry

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SCHEME 2. Procedures for the Alkynylation of Aldehydes with Me_2Zn and Mandelamides

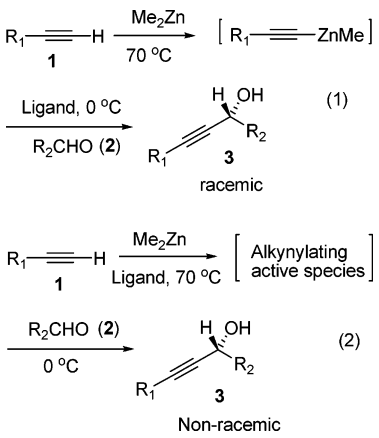

TABLE 1. Results from the Addition of Phenylacetylene to Benzaldehyde (Scheme 1, $R_1 = R_2 = Ph$) in the Presence of Dimethylzinc and Mandelamides I−V[a]

entry	ligand	solvent	*T* (°C)	yield (%)[b]	ee (%)[c]
1[d]	**I**	CH_2Cl_2	0	40	18
2	**I**	toluene	0	65	51
3	**II**	toluene	0	80	29
4	**III**	toluene	0	85	50
5	**IV**	toluene	0	85	4
6	**V**	toluene	0	87	31
7	**I**	toluene	50	90	42
8	**II**	toluene	50	88	34
9	**III**	toluene	50	86	65
10	**I**	toluene	70	84	40
11	**II**	toluene	70	91	48
12	**III**	toluene	70	90	70
13[e]	**III**	toluene	70/0	81	3
14[f]	**III**	toluene	70/0	95	89

[a] Benzaldehyde (1 mmol), ligand (0.2 mmol), Me_2Zn (6 mmol), phenylacetylene (7.2 mmol). [b] Yields refer to isolated product after column chromatography. [c] Enantiomeric excesses were determined by HPLC on a Chiralcel OD-H column. [d] The reaction was carried out in the presence of $Ti(O^iPr)_4$. 1-Phenylethanol was also obtained in 55% yield. [e] Reaction according Scheme 2, eq 1. [f] Reaction according Scheme 2, eq 2.

14). Under these conditions (Scheme 2, eq 2), very good yield (95%) and enantioselectivity (89% ee) were obtained.

We also checked the addition of the substrate at different temperatures. However, no improvement was observed at either higher (room temperature) or lower temperatures (−10 or −20 °C). Under the above optimized reaction conditions, ligand **III** was employed to induce the enantioselective addition of phenylacetylene to 2- and 3-furanecarbaldehyde and 2- and 3-thiophenecarbaldehyde.[21] As the results summarized in Table 2 show, good yields (86−95%) and enantioselectivities (83−90% ee) were obtained (entries 2−4), similar to those obtained in the addition to benzaldehyde.

The generality of this catalytic system was examined using two other terminal alkynes. Using the less reactive alkylacetylene (**1b**) instead of phenylacetylene (**1a**), excellent yields were obtained (90−96%) with high enantioselectivities (88−92% ee) in short reaction times (1.5−3.5 h; entries 6−10). We also

TABLE 2. Alkynylation of Benzaldehyde and Heteroaromatic Aldehydes in the Presence of Dimethylzinc and Mandelamide III, According to Scheme 2, Equation 2

entry	alkyne **1** (R_1)	aldehyde **2** (R_2)	t_1 (min)	t_2 (h)	yield (%)[a]	ee (%)[b]
1	**a**, Ph	**a**, Ph	20	1	95	89
2	**a**, Ph	**b**, 2-furyl	20	1	88	83
3	**a**, Ph	**c**, 3-furyl	20	1	94	89
4	**a**, Ph	**d**, 2-thienyl	20	1.5	91	90
5	**a**, Ph	**e**, 3-thienyl	20	2	86	88
6	**b**, $PhCH_2CH_2$	**a**, Ph	30	3	96	88
7	**b**, $PhCH_2CH_2$	**b**, 2-furyl	30	1.5	96	90
8	**b**, $PhCH_2CH_2$	**c**, 3-furyl	30	2.5	93	92
9	**b**, $PhCH_2CH_2$	**d**, 2-thienyl	30	3.5	90	91
10	**b**, $PhCH_2CH_2$	**e**, 3-thienyl	30	1.7	94	89
11	**c**, *t*-Bu	**a**, Ph	60	2	93	67
12	**c**, *t*-Bu	**b**, 2-furyl	60	1	79	85
13	**c**, *t*-Bu	**c**, 3-furyl	60	1.5	98	90
14	**c**, *t*-Bu	**d**, 2-thienyl	60	1.5	95	90
15	**c**, *t*-Bu	**e**, 3-thienyl	60	1.5	90	77

[a] Yields refer to isolated product after column chromatography. [b] Determined by HPLC using chiral stationary phases.

studied the highly sterically hindered *tert*-butylacetylene (**1c**), obtaining again very good yields and enantioselectivities. This acetylene is a very challenging substrate, and in fact, the enantioselective addition of *tert*-butylacetylene to benzaldehyde with an 80% yield and 53% ee reported by Jiang[22] is the only successful example reported so far. It is worth remarking that with our catalytic system this reaction gave improved 93% yield and 67% ee of the corresponding propargylic alcohol (entry 11). More interesting, the results are still better with heteroaromatic aldehydes **2b**−**e**, specially with regards to the enantioselectivity of the reaction (77−90% ee; entries 12−15).

The stereochemistry of the propargylic alcohols resulting from the addition of phenylacetylene (**1a**) and 4-phenyl-1-butyne (**1b**) was assigned by comparison of the optical rotations and retention times in HPLC with values reported in the literature for **3aa**, **3ac**, and **3ba**.[23] According to that, the configuration of the stereogenic center in **3aa** and **3ba** derived from benzaldehyde must be *R*. If we assume that the sense of the enantioselectivity with the heteroaromatic aldehydes is the same as with benzaldehyde, the configuration of the stereogenic center in compounds **3ab**−**3ae** and **3bb**−**3be** should be *S* because of the change in the priority order when applying the CIP rules.[24]

In summary, we have developed a new procedure for the enantioselective addition of terminal alkynes to heteroaromatic aldehydes, affording high yields and enantioselectivities of heterocyclic propargylic alcohols. An advantage of our system is that the catalysts are easily prepared in a one-step procedure, and a modular design of the catalyst is possible by varying the starting hydroxy acid and amine; also, both enantiomers of the catalyst are available from the corresponding mandelic acid and α-methylbenzylamine enantiomers. Furthermore, the reaction times are short, and unlike most other described procedures, using mandelamide **III** does not require the addition of $Ti(O^iPr)_4$.

(20) We assume that the formation of the mandelamide−Zn complex involves deprotonation of the mandelamide, which is carried out by Me_2Zn (see ref 16). The preformed alkynylzinc reagent may be not basic enough to achieve this deprotonation.

(21) Attempts of addition to *N*-methyl-2-pyrrolecarbaldehyde gave complex reaction mixtures.

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(23) A comparison with the *tert*-butylacetylene addition products **3ca**−**3ce** was not possible.

(24) The optical rotation signs and HPLC retention times of compounds **3aa**, **3ac**, and **3ba** synthesized here coincide with those reported by Shibashaki in ref 13. In that article, the stereochemistry of **3ac** is reported as being *R*, probably because of a distraction in the application of the CIP rules. However, Shibashaki's product is described as being *S* in Scifinder.

Experimental Section[25]

General Procedure for the Catalytic Asymmetric Alkynylation of Aldehydes. A 2 M solution of Me_2Zn in toluene (3 mL, 6 mmol) was added to a solution of alkyne **1** (7.2 mmol) in dry toluene (5 mL), under argon at room temperature. After 15 min, a solution of ligand **III** (83 mg, 0.2 mmol) in dry toluene (2 mL) was added, and after 15 min at room temperature, the solution was heated at 70 °C until the formation of a white precipitate in the solution was formed (20 min for alkyne **1a**, 30 min for alkyne **1b**, and 60 min for alkyne **1c**). Then, the reaction mixture was cooled to 0 °C, and aldehyde **2** (1 mmol) was added. After the reaction was complete (TLC), 1 M HCl (20 mL) was added (CAUTION! Gas evolution) and the reaction extracted with diethyl ether (3 × 15 mL). The organic layer was washed with brine, dried, concentrated, and chromatographed on silica gel to give compound **3**.

(25) For a description of the general experimental methods, see the Supporting Information.

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Supporting Information Available: Experimental general methods, characterization data, ^{1}H NMR and ^{13}C NMR spectra for compounds **3** and ligand **V**. This material is available free of charge via the Internet at http://pubs.acs.org.

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