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Synergistic Copper/Enamine Catalysis for the Regio-, Stereo- and Enantioselective Intermolecular α -Addition of Aldehydes to Allenamides

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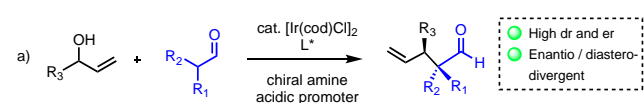
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KEYWORDS : Synergistic catalysis; α -Addition; Allenes; Copper; Enamine

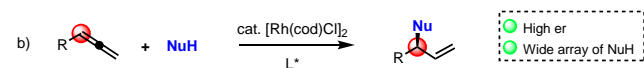
ABSTRACT: We herein describe an intermolecular enantioselective α -addition of aldehydes to allenamides, using a dual copper / enamine catalytic system. Highly enantioselective addition of aldehydes were obtained thanks to secondary amine catalysts. The process was found to be highly regio-, stereo- and enantio-selective under mild conditions.

Synergistic catalysis has recently emerged as a powerful tool in organic synthesis, by combining the divergent reactivity of two distinct catalytic systems in a single reaction mixture.¹ In the last decade, the combination of transition-metal catalysis with amine organocatalysts through imine or enamine species has been exploited to develop efficient methods for the preparation of synthetically relevant building blocks.²⁻³ Recently, the Carreira group has developed a strategy based on the combination of chiral amine catalyst and chiral iridium catalyst. This method has shown outstanding results in the context of enantioselective allylic substitution of aldehydes (scheme 1a),⁴ affording high enantio- and diastereo-divergence. This reaction was successfully applied to the synthesis of several diastereomer of tetrahydrocannabinols,^{4c} showcasing the synthetic potential of synergistic catalytic processes.

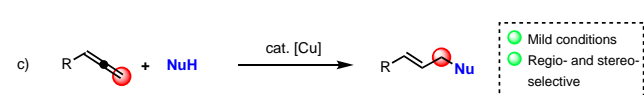
Carreira^{4a}: Synergistic Ir / enamine catalysis



Breit^{5a}: Rh-catalyzed enantioselective Markovnikov addition to allenenes



Our group^{6a}: Cu-catalyzed anti-markovnikov addition to allenenes

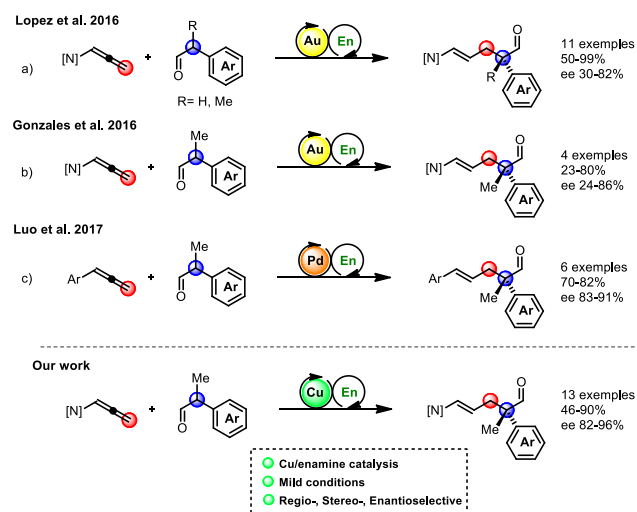


Scheme 1. Works of Carreira, Breit and our group

However, such a strategy may suffer from the use of acidic promoter (carboxylic or phosphoric acids), which in turn leads to a loss of atom economy. In order to address the atom economy issues associated with classical "Tsuji-Trost-type" allylation processes, Breit and coworkers has developed a range of enantioselective branched-selective reactions based on rhodium-

catalyzed additions of various nitrogen, oxygen, sulfur and carbon-based nucleophiles to terminal allenenes (scheme 1b).⁵ In parallel, our research group also reported the addition of nitrogen, oxygen and carbon nucleophiles to terminal allenamides using a copper catalyst (scheme 1c). Unlike Breit's work, exclusive regioselectivity for the linear product was observed in our conditions, owing to the addition of the nucleophile in the distal C=C bond.⁶

In our quest for the development of enantioselective copper-catalyzed transformations, we then set out to examine whether the use of carbonyl pronucleophiles (aldehydes) in the presence of a chiral amine catalyst afford the addition to terminal allenamides in a synergistic catalytic process (scheme 2).

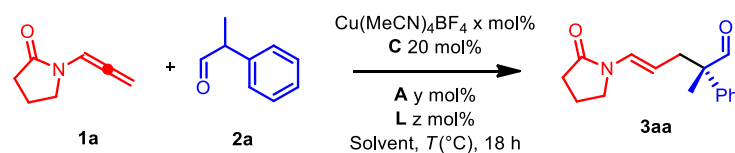


Scheme 2. Synergistic transition metal-enamine catalyzed anti-Markovnikov addition of aldehydes

Such synergistic catalysis-based enantioselective functionalizations of allenes have been reported only using precious transition-metal catalysts such as rhodium,⁷ palladium (scheme 2c)⁸ or gold (scheme 2a-b)⁹ and thus represents a challenging area of research. In particular, previous works on the enantioselective addition of aldehydes to allenamides catalyzed by a gold /enamine system was performed with limited efficiency,

of an α -carbonyl quaternary stereocenter is of paramount importance in enantioselective catalysis.¹¹

as the desired products were obtained in low yields and/or enantioselectivity (68-83% ee with yields ranging from 23-53%).^{9b} Thus, this reaction represents a significant synthetic challenge, especially in its enantioselective version. The functionalization of allenamide derivatives via distal addition is of high importance, as enamine products are chemical intermediates of high synthetic value.¹⁰ In addition, the generation



entry	solvent	x mol %	A (y mol %)	L (z mol %)	C	tempera- ture	3aa Yield % ^b	e.r. ^c
1	THF	20	A ₁ (0)	L ₁ (0)	C ₁	70	62	46:54
2	toluene	20	A ₁ (0)	L ₁ (0)	C ₁	70	32	37:63
3	toluene	20	A ₁ (0)	L ₁ (0)	C ₁	60	16	21:79
4	toluene	20	A ₁ (20)	L ₁ (0)	C ₁	60	28	16:84
5	toluene	20	A ₁ (20)	L ₁ (20)	C ₁	60	46	12:88
6	toluene	20	A ₁ (20)	L ₁ (20)	C ₂	60	48	50:50
7	toluene	20	A ₁ (20)	L ₁ (20)	C ₃	60	35	15:85
8	toluene	20	A ₁ (20)	L ₁ (20)	C ₄	60	10	Nd
9	toluene	20	A ₁ (20)	L ₁ (20)	C ₅	60	39	5:95
10	toluene	20	A ₁ (20)	L ₁ (20)	C ₆	60	27	49:51
11	toluene	20	A ₁ (20)	L ₁ (20)	C ₇	60	33	28:72
12	toluene	20	A ₁ (20)	L ₁ (20)	C ₈	60	67	25:75
13	toluene	20	A ₁ (20)	L ₂ (20)	C ₅	60	65(58)	4:96
14	toluene	20	A ₁ (20)	L ₃ (20)	C ₅	60	12	Nd
15	toluene	20	A ₁ (20)	L ₄ (20)	C ₅	60	22	8:92
16	toluene	20	A ₁ (20)	L ₅ (20)	C ₅	60	41	4:96
17	PhCl	20	A ₁ (20)	L ₂ (20)	C ₅	60	63	4:96
18	PhCF ₃	20	A ₁ (20)	L ₂ (20)	C ₅	60	88(86)	5:95
19	Mesitylene	20	A ₁ (20)	L ₂ (20)	C ₅	60	47	3:97
20	THF	20	A ₁ (20)	L ₂ (20)	C ₅	60	87(81)	13:87
21	PhCF ₃	10	A ₁ (20)	L ₂ (10)	C ₅	60	30	8:92
22	PhCF ₃	10	A ₂ (20)	L ₂ (10)	C ₅	60	25	Nd
23	PhCF ₃	10	A ₃ (20)	L ₂ (10)	C ₅	60	39	5:95
24	PhCF ₃	10	A ₄ (20)	L ₂ (10)	C ₅	60	60	8:92
25	PhCF ₃	10	A ₅ (20)	L ₂ (10)	C ₅	60	72	15:85
26	PhCF ₃	20	A ₅ (20)	L ₂ (20)	C ₅	60	76	12:88

^a reaction performed with 0.25 mmol of **1a** and 0.50 mmol of **2a**. ^b Assessed by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard. ^c Assessed by chiral HPLC on isolated product.

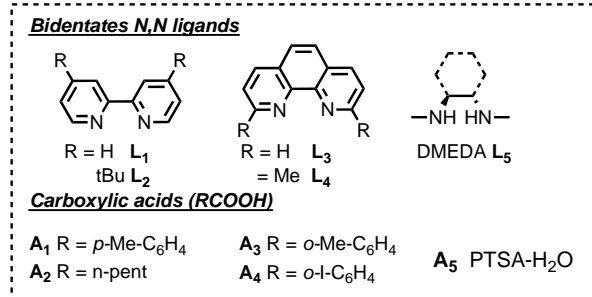
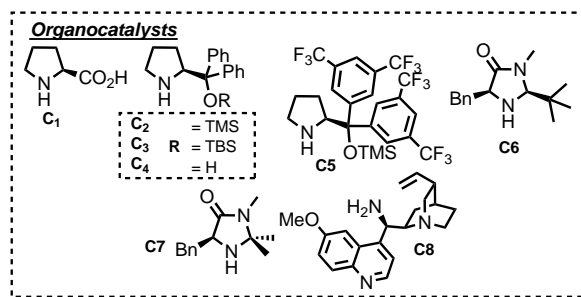
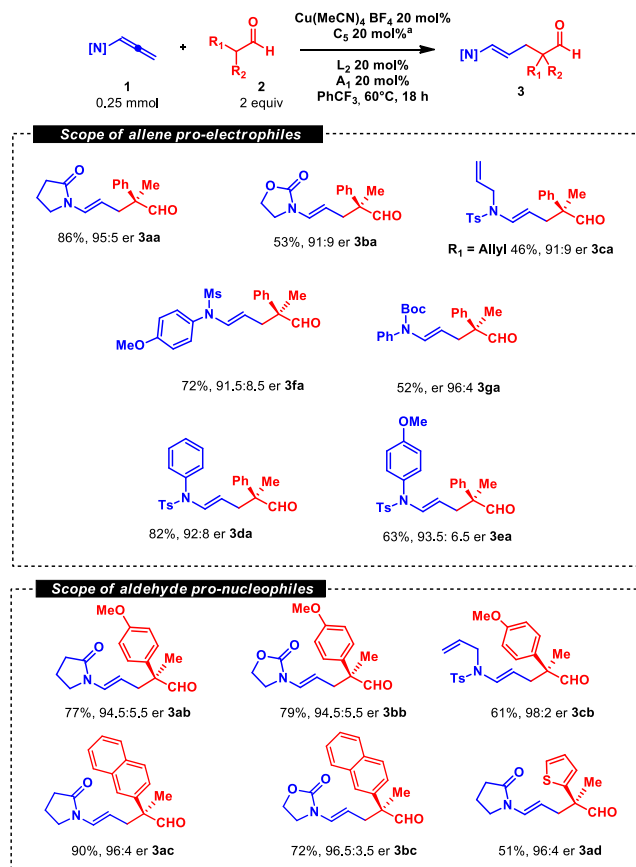


Table 1. Selected data for reaction parametric study.^a

To test our hypothesis, we reacted allenamide **1a** with aldehyde **2a** in the presence of Cu(MeCN)₄BF₄ and aminocatalysts (table 1). We selected aldehyde **2a** to avoid the formation of amine-catalyzed aldol oligomerization products. When **1a** was heated at 70°C in THF in the presence of diphenylprolinol trimethylsilyl ether **C₁** as the chiral amine catalyst, the desired product **3aa** was obtained in good yield (62%), complete regio- (exclusive addition of the carbon atom of the distal C=C bond) and stereo-selectivity (only the *E* alkene was obtained),⁶ but with very modest enantioselectivity (46:54) (table 1, entry 1). When the solvent was changed to toluene, the enantioselectivity could be increased (37:63), although the reactivity of the catalytic system was decreased (entry 2). At a slightly lower reaction temperature (60°C), the yield dropped down to 16%, but the enantioselectivity was largely improved (er = 21:79, entry 3). We then hypothesized that the use of a catalytic amount of weak acid would enhance the organocatalyst activity by accelerating the enamine formation, with limited risk of hydrocarboxylation of the allenamides at the working temperature in the absence of an inorganic base.^{6f} However, when 20 mol% of *p*-methylbenzoic acid **A₁** was added, the yield and enantioselectivity were only slightly improved (28% and 16:84 respectively, entry 4). Then, we thought that the addition of external nitrogen ligand would prevent the potential formation of (prolinol) copper (I) complex,¹² which could sequester the organocatalyst in such non-polar, weakly coordinating solvent as toluene. Indeed, with a combination of 20 mol% of **A₁** and 2,2'-bipyridine **L₁**, the yield and enantioselectivity were further improved to 46% and 88:12 er, respectively (entry 5). With these conditions in hand, we screened a range of commercially available amine catalysts (entries 6-12). Although L-proline gave essentially racemic mixture (entry 6), prolinol based organocatalysts (**C₃**, **C₅**) gave the best enantioselectivities, with **C₅** giving an excellent enantiomeric ratio of 95.5:4.5, albeit affording **3aa** in a somewhat lower yield (entry 9). Both McMillan-type catalysts (**C₆**-**C₇**) and cinchona alkaloids-derived amine catalyst **C₈** gave lower enantioselectivity (entry 10-12). Using the conditions depicted in entry 9, we tested other parameters, such as the ligand, the solvent, and the acid additive (table 1). When, 4,4'-ditert-butyl-2,2'bipyridine **L₂** was used, the yield could be increased up to 65% (58% isolated yield) without affecting the enantioselectivity (entry 13). When other nitrogen ligands were screened (entries 14-16), similar high enantioselectivities were obtained, but phenanthroline and diamine ligands afforded lower amount of the desired product. With aromatic solvents product **3aa** was obtained in similar high enantioselectivities (entries 17-19). In particular, α,α,α -trifluorotoluene afforded **3aa** in high isolated yield (86%, entry

18), and with excellent enantiomeric ratio (95:5 er). Using THF as the solvent, the enantioselectivity was decreased to 87:13 er (entry 20). Further attempts to optimize the reaction by screening carboxylic acid co-catalysts (**A₁₋₅**) at lower copper/ligand loadings were engaged (entries 21-26). Indeed, increasing the acidity of the proton resulted in the improvement of the yield of **3aa**, but it was accompanied with a substantial loss of enantioselectivity in the case of stronger acids. Rate acceleration of the background enol addition to the unsaturated substrate under strong Brønsted acid conditions might account for this result.¹³

We then started to study the scope of this reaction by using the optimized conditions (table 1, entry 18) and screened a range of allenamides **1a-1g** with the model aldehyde reagent **2a** (scheme 3) in order to evaluate the influence of the substitution pattern on the nitrogen atom. When N-allenyl oxazolidinone **1b** was selected as the substrate, similar enantioselectivity (91:9) was obtained, although the yield of the desired product (**3ba**) decreased when compared with **3aa**. We also observed that other electron-withdrawing protecting groups on the nitrogen atom such as tosyl (**1c**, **1d-e**), mesyl (**1f**) or tert-butylloxycarbonyl (Boc) (**1g**) afforded high enantioselectivities (>80% ee) of the adduct regardless of the substitution on the nitrogen atom. However, it is worth noting that carbonyl-substituted allenamides (**1a-b**) seem to react with similar high enantioselectivity than sulfonyl-substituted ones. Indeed, while allyl substituted allenamide **1c** yielded the adduct in moderate yield (**3ca**, 46%) aryl-substituted analogs afforded higher amounts of the desired product (**3da-3ea**, 82-63%). The preparation of **3ca** was accompanied with the formation of unidentified side-product which resulting from reactions of the pending allyl moiety. When comparing the sulfonyl protecting groups, similar yields were obtained when switching from tosyl (**3ea**) to mesyl (**3fa**). Surprisingly, the use of Boc-protected allenyl carbamate also afforded the desired product (**3ga**) albeit in moderate yield (52%). The fact that the reaction conditions are compatible with such an acid sensitive nitrogen protecting group is remarkable, since Boc protecting group can be easily cleaved even under mild Lewis acidic copper(I) catalyzed conditions.¹⁴

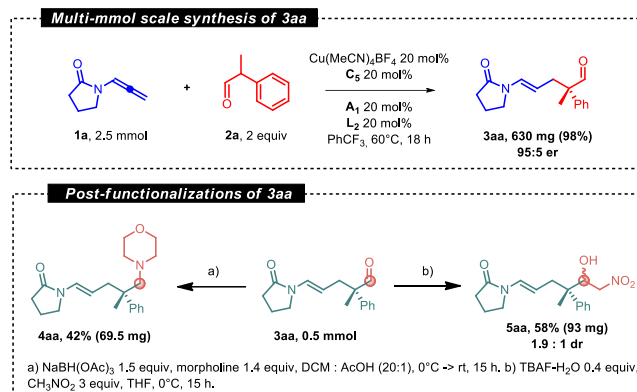


Scheme 3. Scope of allenamide substrates and aldehydes nucleophiles (yield values are those of the pure isolated products)

Next, we turned our attention to the influence of aldehyde partner. We were pleased to observe that aryl(methyl) **2a-b**, aryl(naphthyl) **2c** and heteroaryl(methyl) **2d** α -substituted aldehydes were found to be effective in this reaction. In nearly all cases, excellent enantioselectivities were obtained ($\geq 89\%$ ee). Quite remarkably, using *p*-methoxyphenyl substituted aldehyde **2b**, good yields were obtained regardless of the nature of the allenamide partner (**3ab-3cb**). Using aldehyde **2b**, the addition product **3cb** was obtained in an excellent 98:2 enantiomeric ratio, highlighting once again the high enantioselectivity of the process.

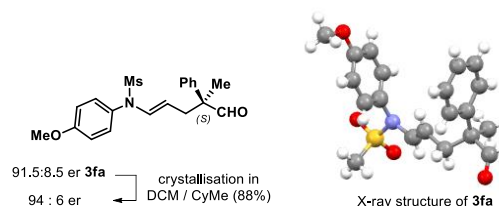
To further demonstrate the synthetic potential of the process, we also set up a multi-millimole scale reaction. Indeed, the tenfold scale-up synthesis of **3aa** afforded the product with nearly quantitative yield (98%, 630 mg) and essentially identical enantioselectivity (95:5 er). Furthermore, we performed post-functionalization reactions of the aldehyde moiety to show the synthetic applicability of the optically active aldehyde products. Surprisingly, such sterically hindered α -quaternary aldehydes could be easily functionalized under mild conditions. When performing the reductive amination of **3aa** using morpholine under mild reducing conditions (with sodium tri(acetoxy)borohydride as the reducing agent at room temperature), the desired δ -amino alkene product **4aa** featuring a stereogenic carbon center in the β -position was obtained in moderate yield (42%). The Henry reaction of **3aa** with ni-

tromethane under mildly basic conditions (TBAF-H₂O) afforded the desired nitroaldol product **5aa** in moderate yield and diastereo-selectivity (58%, 1.9:1 dr).



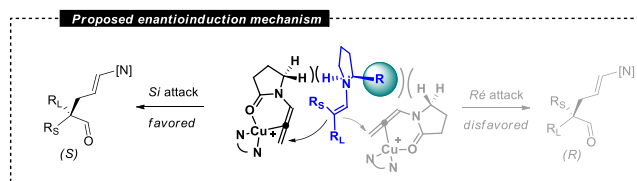
Scheme 4. Scale-up synthesis of **3aa** and post-functionalization reactions

To gain information on the stereochemistry of the allylation process, we have performed X-ray diffraction of **3fa**. Indeed, needle-like crystals of **3fa** could be obtained when crystallizing at 0°C in a DCM / CyMe mixture. X-ray diffraction analysis showed that **3fa** was obtained with *S* configuration on the quaternary carbon center (scheme 5).



Scheme 5. X-ray structure of **3fa** (ellipsoids are given with 50% probability) and proposed stereochemical model for the enantio-determining step

According to the observed absolute configuration of **3aa**, we propose a stereochemical model (scheme 6) in which the addition of the chiral enamine (resulting from the addition of the Hayashi-Jorgensen catalyst on the aldehyde) occurs from the *Si* face of the (*E*)-enamine (backside attack). Indeed, such a backside attack should be favored to minimize the steric repulsion between both the substituents on the nitrogen atom of the allenamide and the bulky aryl group on the prolinol catalyst, consistently with the proposed stereochemical models used in prolinol-based enamine catalysis¹⁵.



Scheme 6. Proposed stereochemical model for the enantio-determining step

To conclude, we have developed a highly enantioselective method for the addition of aldehydes pronucleophiles to allenamides. To achieve this goal, a combination of two synergistic catalytic systems based on copper and chiral amine catalysts was found to be highly efficient. Using cheap, readily available, and environmentally benign catalysts (cationic copper (I) complex and Hayashi-Jorgensen prolinol), high regio-, stereo- and enantio-selectivities were obtained. The reaction could be scaled up to multi millimole scale without any loss of the catalyst activity and selectivity. We are currently investigating other enantioselective additions of various nucleophiles to allenes by means of copper catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information (containing all the NMR spectra, chiral HPLC chromatograms of all the described products, as well as the procedures to prepare both starting materials and products) is available free of charge on the ACS Publications website. FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for all compounds.

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Author Contributions

†These authors equally contributed to this work. The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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