Regio-, Stereo- and Enantioselective α-Addition of Carbonyl Nucleophiles to Allenamides Catalyzed by a Synergistic Copper/Enamine System

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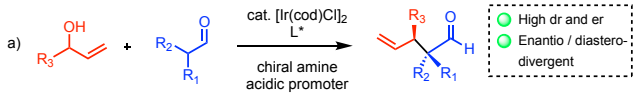
Supporting Information Placeholder

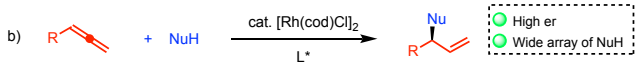
ABSTRACT: A dual copper/enamine catalytic system is found to enable an intermolecular enantioselective α-addition of various carbonyl nucleophiles to allenamides. Secondary amine catalysts allowed the highly enantioselective addition of aldehydes, while using primary amine catalysts led to the enantioselective addition of ketoester nucleophiles. The process was found to be highly regio-, stereo- and enantio-selective and represented the first allene hydrofunctionalization using an synergistic catalysis involving copper.

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 particular, the combination of transition-metal catalysis with amine organocatalysts through imine or enamine species has recently been exploited to develop new efficient synthetic methods for the formation of useful building blocks.[2-3] Recently, the combination of chiral amine catalyst and chiral iridium catalyst has shown impressive results in the context of enantioselective allylic substitution of aldehydes (scheme 1a).[4] One of the particular features of this reaction is the very high diastereo-divergence of the process, which has been successfully applied to the synthesis of several diastereomer of tetrahydrocannabinols.[4c]

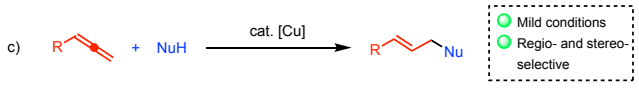
Carreira[4]: *Catalyst-controlled synergistic Ir / enamine catalysis*



Breit[5]: *Rhodium catalyzed enantioselective Markovnikov addition to allenes*

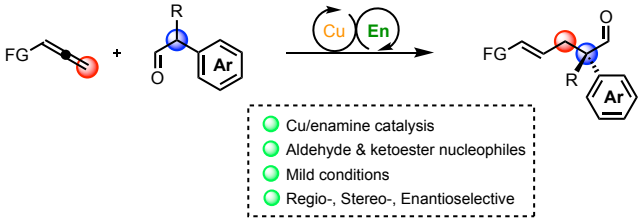


Our group[6]: *Copper catalyzed anti-markovnikov addition to allenes*



Scheme 1. Representative examples of synergistic catalysis and of hydrofunctionnalization of allenes.

In order to address the atom economy issues in allylation processes, the hydrofunctionalization has recently emerged as a powerful strategy. A representative example is the work performed by the Breit research group, developping a range of enantioselective branched-selective reaction based on rhodium-catalyzed additions of various nucleophiles to terminal allenes (scheme 1b).[5] In parallel, our research group also reported the addition of nitrogen, oxygen and carbon nucleophiles to terminal allenes using a copper catalyst (scheme 1c).[6] In our conditions, exclusive regioselectivity for the linear product was observed, owing to the addition of the nucleophile in the distal C=C bond. In our quest for the development of enantioselective copper-catalyzed transformations, we envisioned the possibility of using carbonyl pronucleophiles in the presence of a chiral amine catalyst to perform the addition to terminal allenamides in a synergistic catalytic process (scheme 2).

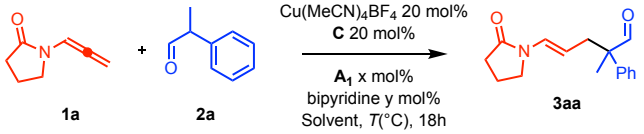


Scheme 2. This work: synergistic Cu-enamine catalyzed anti-Markovnikov addition of aldehydes

Indeed, such synergistic catalysis-based enantioselective functionalization of allenes has been reported only by the use of precious transition-metal catalysts such as palladium[7] or gold[8] and thus represents a challenging area of research. More specifically, functionalization of allenamide derivatives via distal addition is of high importance, as enamine products are intermediates of high synthetic value[9].

To test our hypothesis, we reacted allene **1a** with aldehyde **2a** in THF in the presence $Cu(MeCN)_4BF_4$ and Hayashi-Jorgensen type amine catalysts $\mathbf{C_2}$-$\mathbf{C_5}$ (Table 1). When **1a** was heated at 70°C in THF in the presence of diphenylprolinol trimethylsilyl ether $\mathbf{C_2}$ as chiral amine catalyst, the desired product was obtained in good yield but with very modest enantioselectivity (Table 1, entry 1). Switching the solvent to toluene increased the enantioselectivity, although the reactivity of the catalytic system was decreased (Table 1, entry 2). The reaction temperature was lowered to 60°C, leading to a low yield of 16%, but the enantioselectivity was largely improved (Table 1, entry 3). In order to increase the catalyst turn-over, we hypothesized that the addition of external nitrogen—based ligand (as 2,2'-bipyridine) would prevent the potential formation of (prolinol)copper (I) complex.[10] We thought that this stable specie would sequestrate the organocatalyst and thus would be responsible for the drop of catalytic activity in such non-polar, weakly coordinating solvent as toluene. Furthermore,

we thought that the use of a catalytic amount of weak acid (RCOOH) could enhance the organocatalyst activity by accelerating the enamine formation, without any risk of hydrocarboxylation of the allenamides at 60°C in the absence of a base.[6f] When 20 mol% of *p*-methylbenzoic acid **A_1** was added as the sole additive, the yield and enantioselectivity were slightly improved (Table 1, entry 4). When a combination of 20 mol% of **A_1** and 2,2'-bipyridine **L_1** acting as copper ligand, the yield and enantioselectivity were further improved to 46% and 88:12 er, respectively (Table 1, entry 5). With these new conditions in hand, we tried to find the most suitable organocatalyst, using a range of commercially-available amine catalysts. Although, L-proline **C1** gave essentially racemic mixture (entry 6), prolinol based organocatalysts (**C_2-C_5**) gave the best enantioselectivity, with **C_5** giving an excellent enantiomeric ratio of 95.5:4.5, although giving **3aa** in somewhat lower yield (Table 1, entry 9). McMillan-type catalysts (**C_6-C_7**) and Cinchona Alkaloids-derived amine catalyst **C_8** gave lower enantioselectivity (Table 1, entry 10-12).



Entry	Solvent	x	y	C	T	yield%[b]	er[c]
1	THF	0	0	C_2 (20)	70	62	45.5 : 54.5
2	Toluene	0	0	C_2 (20)	70	32	37 : 63
3	Toluene	0	0	C_2 (20)	60	16	20.5 : 79.5
4	Toluene	20	0	C_2 (20)	60	28	15.5 : 84.5
5	Toluene	20	20	C_2 (20)	60	46	12 : 88
6	Toluene	20	20	C_1 (20)	60	48	50 : 50
7	Toluene	20	20	C_3 (20)	60	35	15 : 85
8	Toluene	20	20	C_4 (20)	60	10	nd
9	Toluene	20	20	C_5 (20)	60	39	4.5 : 95.5
10	Toluene	20	20	C_6 (20)	60	27	49 : 51
11	Toluene	20	20	C_7 (20)	60	33	27.5 : 72.5
12	Toluene	20	20	C_8 (20)	60	67	24.5 : 75.5

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol) in 0.5 mL of solvent, 18h. [b]Assessed by ^{1}H NMR using 1,3,5 trimethoxybenzene as the internal standard [c]Assessed by chiral HPLC (Chiralcel OD-H, 95:5 Hex:IPrOH, 1.5ml/min) on isolated product.

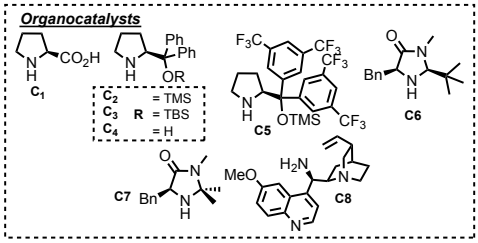
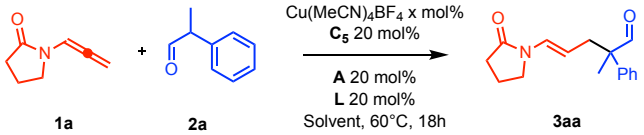


Table 1. Preliminary catalyst screening

With catalyst **C_5** in hand, we then tried to find the best combination of solvent, ligand and acid additive (Table 2). When, 4,4'-ditert-butyl-2,2'bipyridine **L_2** was used, the yield could be increased up to 65% (58% isolated yield) without affecting the enantioselectivity (Table 2, entry 2). Overall, although the nature of L ligand on copper did not affect the enantioselectivity, large reactivity differences were observed, with bipyridines **L_1-L_2** and diamines (Table 2, entries 1-2, 5) giving moderate to good catalytic activity, unlike phenanthroline-based ligands **L_3-L_4** (Table 2, entries 3-4). Next we screened the solvents, and we were pleased to note that the use of aromatic solvents yielded the desired product **3aa** in similar enantioselectivities ranging from 95:5 to 97:3 er (Table 2, entries 6-8). Among these solvents, reaction in α,α,α-trifluorotoluene afforded **3aa** in very high isolated yield (86%, Table 2, entry 7). When THF was used as the solvent, the product was isolated in similar yield as with α,α,α-trifluorotoluene, but the enantioselectivity was decreased to 87:13 er (Table 2, entry 9). Finally, we screened the influence of the acid additive over both reactivity and enantioselectivity, using 10 mol% of $Cu(MeCN)_4BF_4$ as the metal catalyst. An almost linear pKa / reactivity correlation was observed using various carboxylic acids and *p*-toluenesulfonic acid as additives. While **A_1** gave 30% of yield (Table 2, entry 10), stronger acids gave higher yields (39-72%) in the same conditions (Table 2, entries 12-14). However, in the case of strong acid (PTSA **A_5**, Table 2, entries 14-15) this enhancement of catalytic activity was accompanied with a substantial loss of enantioselectivity. Rate enhancement of the background enol addition to the unsaturated substrate under strong Brønsted acid conditions might account for this result.[11]



Entry	Solvent	L	A (pKa)	x	yield%[a]	er[b]
1	Toluene	L_1	A_1 (4.4)	20	39	4.5 : 95.5
2	Toluene	L_2	A_1 (4.4)	20	65(58)	4 : 96
3	Toluene	L_3	A_1 (4.4)	20	12	nd
4	Toluene	L_4	A_1 (4.4)	20	22	7.5 : 92.5
5	Toluene	L_5	A_1 (4.4)	20	41	4 : 96
6	PhCl	L_2	A_1 (4.4)	20	63	4 : 96
7	$PhCF_3$	L_2	A_1 (4.4)	20	88(86)	5 : 95
8	Mesitylene	L_2	A_1 (4.4)	20	47	3 : 97
9	THF	L_2	A_1 (4.4)	20	87(81)	13 : 87
10	$PhCF_3$	L_2	A_1 (4.4)	10	30	8 : 92
11	$PhCF_3$	L_2	A_2 (4.9)	10	25	nd
12	$PhCF_3$	L_2	A_3 (3.9)	10	39	5 : 95
13	$PhCF_3$	L_2	A_4 (3.0)	10	60	8 : 92
14	$PhCF_3$	L_2	A_5 (-6)	10	72	15 : 85
15	$PhCF_3$	L_2	A_5 (-6)	20	76	11.5 : 88.5

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol) in 0.5 mL of solvent, 60°C, 18h. [b]Assessed by ^{1}H NMR using 1,3,5 trimethoxybenzene as the internal standard [c]Assessed by chiral HPLC (Chiralcel OD-H, 95:5 Hex:IPrOH, 1.5ml/min) on isolated product.

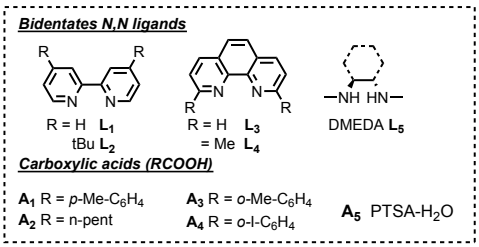
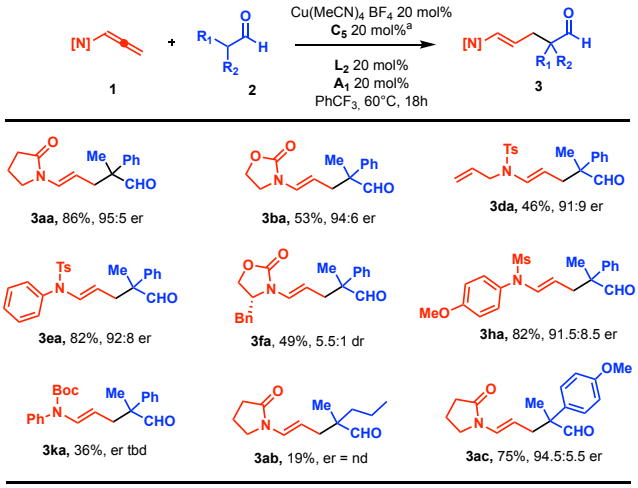


Table 2. Ligand, solvent and acid additive screening

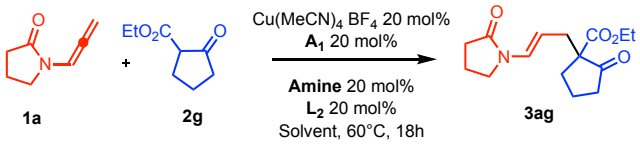
Using our optimized conditions (Table 2, entry 7), we evaluated the scope of the reaction, with a range of allenamides starting materials (scheme 3). When *N*-allenyl oxazolidinone **1b** was used as the substrate, similar enantioselectivity was obtained, although the yield of **3ba** decreased if we compared with **3aa**. We then evaluated the influence of the substitution pattern on the nitrogen atom, obtaining moderate to good yield with *N*-allenyl sulfonamide derivatives **3da**, **3ea** and **3ha**. In order to study catalyst-control versus substrate-control in aldehyde face discriminated, we used two enantiomeric substrates based on *N*-allenyl 4-benzyloxazolidinone **1f**. When the substrate bearing (R) configuration at the carbon center (**1f**) was reacted, moderate yield and good 5.5: 1 diastereomeric ratio (assessed by 1H NMR on the crude mixture) were observed (**3fa**). The (S) substrate (**1g**) gave the same-opposite diastereomer, in a lower-good-excellent xx:1 dr, thus confirming a catalyst-substrate-control with slight-

moderate-high matching-mismatching effect. Product **3ha** was obtained with good yields and high enantiomeric ratio. Finally, we evaluated the substituents on the aldehyde partner. Changing from phenyl to propyl resulted in an important drop of the reactivity, even though the enantioselectivity was maintained.



Scheme 3. Scope of allenamide substrates and aldehydes nucleophiles

In a next set of experiments, we wonder to see if our efficient catalytic system was able to perform the addition of keto-esters to allenamides (Table 3). We took allenamide **1a** and ketoester **2g** as substrate models for the development of the reaction. Starting with previous optimized conditions in table 2, we obtained the targeted compound **3ag** in moderate yield with poor selectivity (Table 3, entry 1). As shown by Luo and coworkers, the reactivity of ketoesters is better with primary amine organocatalyst.[7] So we decided to test several primary amine catalyst $\mathbf{C_8}$-$\mathbf{C_{13}}$ in order to boost the reactivity. In classical conditions, $\mathbf{C_{10}}$ catalyst exhibits excellent reactivity in term of yield but with poor enantiomeric ratio (Table 3, entry 10). To date, diamino catalyst $\mathbf{C_{12}}$ showed moderate conversion but an interesting er of 73:27 (Table 3, entry 12). At the present stage of the studies, we are still preforming the reaction development of the reaction of ketoesters.



Entry	Solvent	Amine	yield%[a]	er[b]
1	$PhCF_3$	$\mathbf{C_5}$	53	48 : 52
2	$PhCF_3$	$\mathbf{C_8}$	21	68 : 32
3	$PhCF_3$	$\mathbf{C_{10}}$	21	60 : 40
4	$PhCF_3$	$\mathbf{C_{12}}$	24	60 : 40
5	$PhCF_3$	$\mathbf{C_9}$	38	46 : 54
6	THF	$\mathbf{C_9}$	33	43 : 57
7	MeCN	$\mathbf{C_9}$	36	27 : 73
8	Toluene	$\mathbf{C_9}$	47	48.5 : 51.5
9	DMSO	$\mathbf{C_9}$	0	nd
10	MeCN	$\mathbf{C_{10}}$	90	50 : 50
11	MeCN	$\mathbf{C_{11}}$	30	71 : 29
12	MeCN	$\mathbf{C_{12}}$	34	73 : 27
13	MeCN	$\mathbf{C_{13}}$	55	53 : 47

[a]Reaction conditions: **1a** (0.25 mmol), **2g** (0.5 mmol) in 0.5 mL of solvent, 60°C, 18h. [b]Assessed by ^{1}H NMR using 1,3,5 trimethoxybenzene as the internal standard [c]Assessed by chiral HPLC (Chiralcel OD-H, 95:5 Hex:IPrOH, 1.5ml/min) on isolated product.

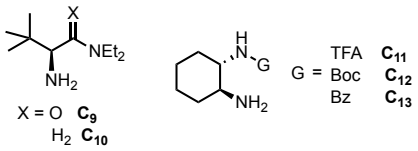


Table 3. Reaction conditions developpement for the addition of ketoesters.

To conclude, we are developing a copper/enamine synergistic system able to perform the addition of aldehydes and ketoesters nucleophiles on allenamides. Studies are still on progress for the development of this unprecedented reaction catalyzed by copper with a large scope of carbonyl nucleophiles.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all new compounds are provided.

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Author Contributions

#These authors contributed equally. 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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