DOI: 10.1002/adsc.201000309

Highly Enantioselective One-Pot Copper-Catalyzed 1,4 Addition/ Organocatalyzed α-Substitution of Enals

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Received: April 21, 2010; Published online: August 16, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000309.

Abstract: The asymmetric copper-catalyzed addition of dialkylzinc to enals followed by organocatalyzed one-pot aldehyde α-functionalization has been accomplished providing C–C, C–Cl or C–F bond formation. These simple procedures led to the creation of two contiguous stereocenters in excellent enantioselectivities (typical *ee* = 99%). This methodology has been applied in the synthesis of (2*S*,3*S*) isomer of Valnoctamide®.

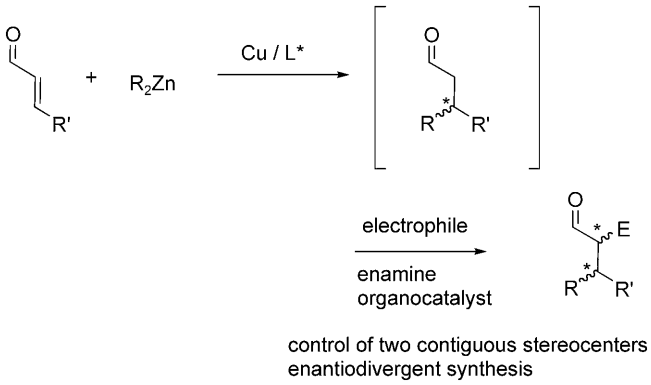
Keywords: copper; enals; enantioselectivity; Michael addition; organocatalysis

Generating high molecular complexity with multiple stereocenters in a minimum of operations is one of the great challenges synthetic chemists are facing. The asymmetric Cu-catalyzed conjugate addition of organometallic reagents with subsequent electrophilic trapping of the enolate generated *in situ*, is one of the methods of choice for such a purpose.[1] Unfortunately, most of these reactions occur on cyclic systems, are often limited in terms of electrophiles scope, and mostly, lead to the formation of only the *trans* diastereoisomer.[2]

Recently, enamine catalysis has emerged as a method of choice for the α-functionalization of carbonyl compounds, notably aldehydes, in high enantioselectivity and with a large scope of electrophiles.[3] Furthermore, this methodology has already shown widespread applications in cascade reactions due to the high compatibility of the reaction system.[4] Thus combining an enantioselective copper-catalyzed Michael reaction with an asymmetric enamine organocatalytic step would easily lead to highly functionalized enantioenriched compounds.[5]

Recently, our group reported the first enantioselective copper-catalyzed addition of organometallic reagents to α,β-unsaturated aldehydes. This reaction leads cleanly to the 1,4 adduct under relatively mild and simple conditions (use of BINAP, at 0 to −20 °C), but unfortunately with relatively modest enantioselectivities (around 90:10 *er*).[6]

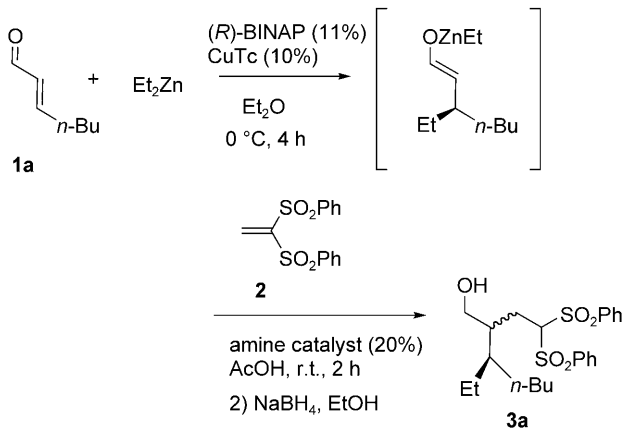
Thus, enantioselectivities in the case of two contiguous stereocenters should be improved by combining the Cu-catalyzed reaction with an enamine step (Scheme 1). There are several advantages in carrying

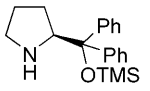


Scheme 1. Proposal for the one-pot copper/enamine reactions.

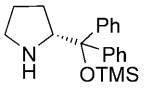
out these two reactions in a one-pot process. First, it could improve the overall yield, particularly when volatile aldehyde intermediates are involved. Furthermore, another of the great advantage would be its application in enantiodivergent synthesis. Indeed, by switching the enantiomers of copper ligand/organocatalyst, each pair of enantiomers and diastereoisomers could be obtained.[4a,7]

In a preliminary experiment, the conjugate addition of diethylzinc to *trans*-2-heptenal, catalyzed by copper thiophene carboxylate (CuTC) with (*R*)-BINAP, was followed by trapping with the highly electrophilic vinyl sulfone **2** (Scheme 2).[8] Without any amine cata-

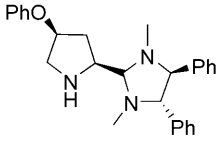




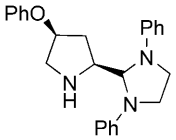
4a,
71% yield
syn/*anti*: 85/15
99% *ee* (*syn*)
94% *ee* (*anti*)



4b,
62% yield
syn/*anti*: 18/82
99% *ee* (*anti*)
80% *ee* (*syn*)



4c,
76% yield
syn/*anti*: 81/19
98.5% *ee* (*syn*)
62% *ee* (*anti*)



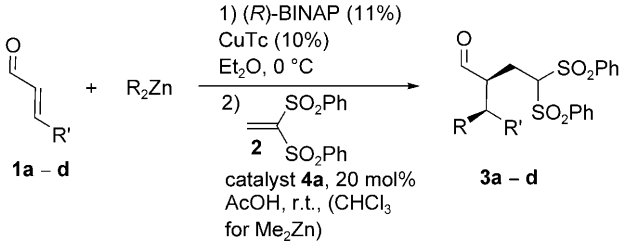
4d,
80% yield
syn/*anti*: 82/18
99% *ee* (*syn*)
82% *ee* (*anti*)

Scheme 2. Preliminary attempts using vinyl sulfone **2**.

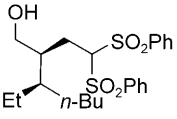
lyst, direct quenching of the zinc enolate did not lead to any diastereocontrol ($dr = 1/1$) with the formation of numerous side products. However, when commercial (*S*)-TMS-protected diphenylprolinol catalyst **4a** was used (after quenching of the zinc enolate by addition of acetic acid), excellent enantioselectivity (99% *ee*) was obtained for the *syn* isomer with a good 71% isolated yield.[9] Using the (*R*)-enantiomer **4b**, the *anti* adduct was formed predominantly with also an excellent 99% *ee* confirming the reaction potential in enantiodivergent synthesis. Using aminal-pyrrolidine catalysts **4c** and **4d**, which already gave excellent results in such additions, also led to the same levels of enantioselectivity together with slightly higher yield.[10]

Since the two enantiomers of TMS-protected diphenylprolinols **4a** and **4b** are cheap and commercially available, this catalyst has been chosen to study the scope of the reaction.

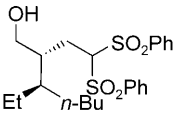
Structurally different alkyl enals and diethyl- or dimethylzinc were then tested in this reaction (Scheme 3). As expected, excellent enantioselectivities for the one-pot procedure were obtained in all cases (99% *ee*). Small alkyl substituents ($R' = Me$) as well as bulky ones ($R' = i\text{-Pr}$) could be used leading to



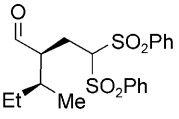
Et_2Zn:



3a[a]
71% yield
syn/*anti*: 85/15
99% *ee* (*syn*)

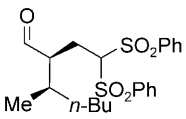


3a[a,b]
62% yield
anti/*syn*: 82/18
99% *ee* (*anti*)

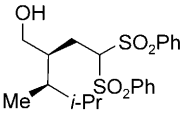


3d[c]
74% yield
anti/*syn*: 75/25
99% *ee* (*anti*)

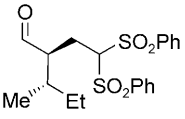
Me_2Zn:



3b
57% yield
syn/*anti*: 83/17
99% *ee* (*syn*)



3c[a]
64% yield
syn/*anti*: 81/19
99% *ee* (*syn*)



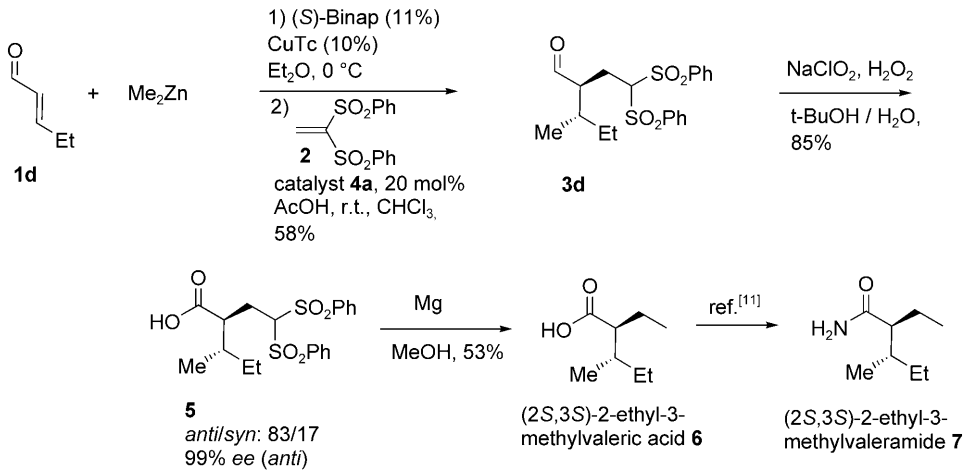
3d[c,d]
58% yield
anti/*syn*: 83/17
99% *ee* (*anti*)

[a] After reduction using $NaBH_4$ for chiral SFC separation.
[b] Catalyst **4b** used.
[c] The *ee* was determined on the corresponding carboxylic acid.
[d] Use of (*S*)-BINAP.

Scheme 3. Scope of the one-pot addition to sulfone **2**.

the same range of yields (57 to 71%) and diastereoselectivities ($dr = 75/25$ to $85/15$). It must be pointed out that chloroform had to be added for the second step when Me_2Zn was used for a better solubilization of the mixture. Furthermore, by choosing the appropriate catalyst/ligand combination, one can synthesize either the *syn* or the *anti* isomer.

To demonstrate the utility of the methodology, compound **3d** was applied to the synthesis of (2*S*,3*S*)-2-ethyl-3-methylvaleramide **7** (Scheme 4). This stereoisomer of Valnoctamide® (a mild tranquilizer commercialized as a mixture of four stereoisomers) is currently in preclinical testing and has been prepared by an eight-step synthesis.[11] Oxidation of the aldehyde **3d** followed by removal of the sulfone using Mg/

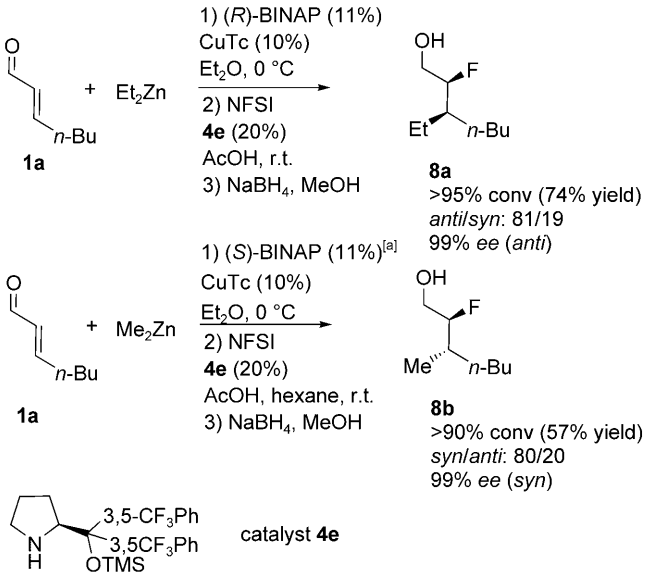


Scheme 4. Application to the synthesis of (2*S*,3*S*) isomer of Valnoctamide® **7**.

MeOH led to (2*S*,3*S*)-2-ethyl-3-methylvaleric acid **6** which can give access in one step to Valnoctamide® as previously reported.[11]

Besides the addition to highly reactive vinyl sulfone **2**, we wondered if this one-pot procedure could be applied to other electrophiles.

We thus turned out our attention to the organocatalytic fluorination (Scheme 5). Gratifyingly, the organocatalytic trapping was also efficient using NFSI as fluorine source.[12] Excellent enantioselectivities were obtained of the fluorinated adduct **8a** using the commercially available BINAP/**4e** catalyst combination. This insertion of fluorine is highly interesting due to the importance of fluorine in medicinal chemistry.[13]



[a] Use of (*S*)-BINAP to form the *syn* diastereoisomer (only isomer separated by chiral GC).

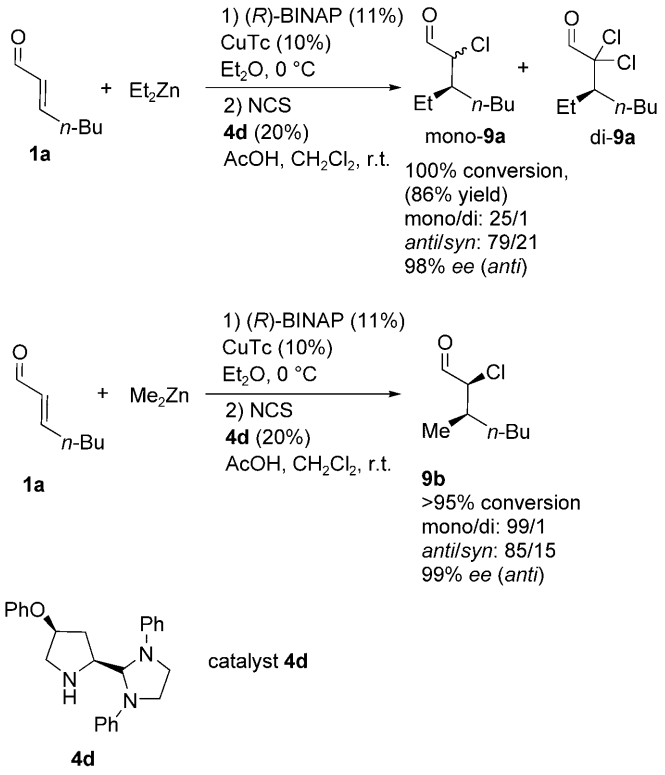
Scheme 5. One-pot Michael/fluorination sequence.

Changing from (*R*)-BINAP to (*S*)-BINAP for aldehyde **1a**, and using dimethylzinc, induced a total reversal from the *anti* to the *syn* adduct **8b**.

Another interesting reaction is the chlorination of aldehydes which can give access to highly versatile molecules.[14] Preliminary experiments using NCS as the chlorinating reagent and various commercial organocatalysts afforded disappointing results (poor conversion, mixture of mono- and di-chlorinated products).[15] Conversely, the direct chlorination of zinc enolates also affords mixture of diastereomers.[2d] Fortunately, using aminal-pyrrolidine catalyst **4d**, a good selectivity for the mono-chlorinated adduct (25/1 to 99/1) was observed together with good enantioselectivities ($ee > 98\%$) using either dimethyl- or diethylzinc reagents (Scheme 6). Furthermore, no other side products were detected in the crude reaction mixture.

Finally, attempts using other electrophiles as a bromine source, DEAD or PhNO failed. PhNO or DEAD decomposed in the reaction mixture while bromination with 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone lead to a 1/1 diastereoisomeric ratio. This is probably due to the racemization of the carbon stereocenter bearing the bromine atom under acidic conditions. Finally, nitroolefins did not give any conversion in the one-pot reaction conditions. It is of course possible to perform the above reactions in a two-pot procedure.

In conclusion, we have disclosed here the first one-pot copper Michael/enamine substitution on enals. Different dialkylzinc nucleophiles in combination with various electrophiles could be used leading to the creation of two stereogenic centers in almost perfect enantioselectivities. Furthermore, the reaction occurs under simple and mild conditions using in most cases cheap commercially available catalysts (BINAP and diaryl-prolinol silyl ethers). This represents the first example of combination of an asymmetric copper-catalyzed step, combined with an enantio-



Scheme 6. One-pot Michael/chlorination sequence.

selective organocatalytic step. Further applications of such combinations toward the synthesis of useful building blocks are currently underway in our laboratory.

Experimental Section

All the relative and absolute configurations were assigned by analogy. Indeed, the absolute configuration of the first copper catalysis step and the different organocatalytic steps are all known.[6,8a,12,14]

General Procedure for the One-Pot Copper Catalysis/Addition to Sulfone

Synthesis of 3d: A solution of 13.1 mg of CuTc (10 mol%/enal), and 46.8 mg of (*S*)-BINAP (11 mol%/enal) in 3.6 mL of diethyl ether was stirred at room temperature for 20 min under argon. The solution was then cooled down to 0 °C before the dimethylzinc (1.32 mmol, 3.3 equiv. (1,2 M in toluene) was added and the solution stirred 15 min at 0 °C. Pentenal (0.66 mmol, 1.65 equiv.) in 1 mL of diethyl ether was then added and the resulting solution stirred at 0 °C for 14 h. 0.35 mL of acetic acid and 1.5 mL of chloroform were then added and the mixture warmed up to room temperature. 20 mol%/sulfone of the TMS-protected diphenyl prolinol (26 mg, 0.08 mmol) and then 120.4 mg of the vinyl sulfone (0.4 mmol, 1 equiv.) were added. The mixture was stirred at room temperature for 2 h before the reaction was quenched by addition of 5 mL of 1 M HCl, The reaction mixture was extracted by three times 10 mL of dichloromethane, the organic layer washed by 5 mL of water, dried over Na_2SO_4 and the solvent evaporated to give the crude product. Purification by flash chromatography using a cyclohexane/ethyl acetate (8/2) mixture afforded the corresponding Michael adduct; yield: 96.0 mg (0.23 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.8$–0.96 (m, 6H), 1.24–1.42 (m, 2H), 1.81–1.85 (m, 1H), 2.08–2.15 (m, 1H), 2.45–2.56 (m, 1H), 3.01–3.12 (m, 1H), 4.70 (dd, major dia, 1H, $J = 6.0$, 3.2 Hz), 4.75 (m, minor dia, 1H), 7.54–7.96 (m, 10H), 9.53 (s, 1H, minor dia), 9.60 (s, 1H, major dia); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.9$ (CH_3), 16.4 (CH_3), 22.1 (CH_2), 26.5 (CH_2), 35.8 (CH), 53.5 (CH), 80.9 (CH), 129.1 (CH), 129.3 (CH), 129.7 (CH), 134.5 (CH), 134.7 (CH), 137.7 (Cquat), 204.1 (CH); MS (ESI): $m/z = 409.3$ $[M+H]^+$; HR-MS (ESI): $m/z = 426.1400$ $[M+NH_4]^+$, calcd. for $C_{20}H_{28}O_5S_2N$: 426.1403.

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[15] See Supporting Information for details.

