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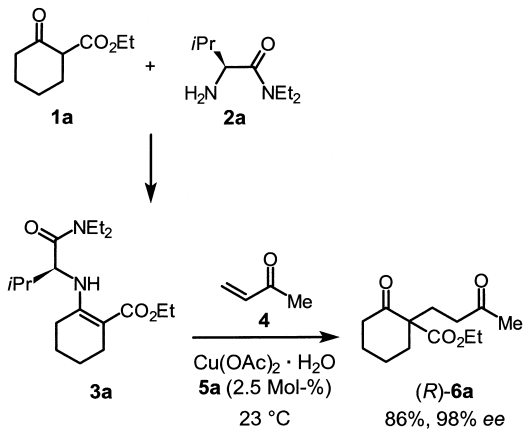
New Chiral Auxiliaries for the Construction of Quaternary Stereocenters by Copper-Catalyzed Michael Reactions**

Jens Christoffers* and Alexander Mann

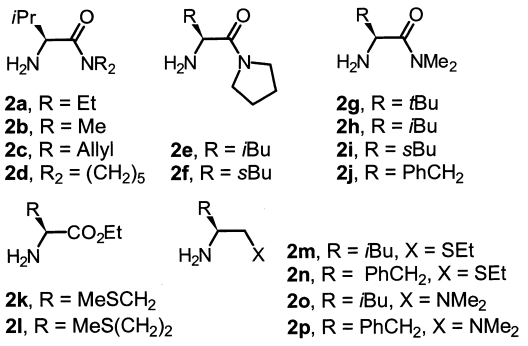
The enantioselective construction of quaternary stereocenters is still a challenging goal in synthetic organic chemistry.[1] Herein we report a new copper(II)-catalyzed and auxiliary-based Michael reaction which allows the construction of quaternary carbon centers with *ee* values in excess of 95% at ambient temperature (see Scheme 1). The Michael reaction is an established method for C–C bond formation and is commonly catalyzed by a strong Brønstedt base.[2] In order to avoid the disadvantages of basic reaction conditions, a number of transition metal catalyzed procedures has been published in recent years; this has resulted in improved chemoselectivity due to the milder reaction conditions.[3] Moreover, chiral ligands can be utilized here to achieve asymmetric catalysis of the Michael reaction. In the recent years a number of chiral catalysts has been reported for the conversion of 1,3-dicarbonyl compounds with α,β-unsaturated ketones.[4] In particular, the introduction of the heterobimetallic lanthanum/sodium/[1,1′-binaphthyl]-2,2′-diol (LSB) catalyst by Shibasaki and co-workers has to be mentioned here as it defines the state of the art in this field.[5] However, the reaction conditions are also Brønstedt basic, and the enantioselective construction of quaternary stereocenters requires low temperatures.

Another strategy is the derivatization of the Michael donor with a chiral amine as an auxiliary to give an imine or enamine, which is subsequently converted with the Michael acceptor.[6] If enamines derived from β-oxoesters are applied according to this method, further activation, by addition of a stoichiometric amount of Lewis acid or by high pressure and low temperature, is required in order to achieve reasonable yields and selectivity.[7] Recently we reported on the Ni-catalyzed conversion of cyclic β-oxoesters in the presence of 1,2-diaminocyclohexane.[8] We were able to prepare the Michael product **6a** in 91% *ee* at ambient temperature and without exclusion of moisture. Similar results can only be achieved with the LSB catalyst at $-50\,^{\circ}C$ (93% *ee*).[9] Koga and co-workers obtained *ee* values of 90% by using a chiral auxiliary and a stoichiometric amount of a Brønstedt base at $-100\,^{\circ}C$.[10] In this work we report on a new class of auxiliaries for the transition metal catalyzed reaction of β-oxoesters **1** with simple enones, such as methyl vinyl ketone (MVK, **4**), and the synthesis of the Michael product **6a** (Scheme 1) with up to 99% *ee* at ambient temperature and without inert conditions, a reaction which is unprecedented in the literature.



Scheme 1. Synthesis of **3a** and the copper(II)-catalyzed conversion with MVK (**4**).

In the course of a combinatorial search,[11] we have investigated a number of chiral amines **2a**–**p** derived from α-amino acids which bear either a thioether, a tertiary amine, or an amide group as an additional donor function.[12, 13] In an



acid-catalyzed reaction with the Michael donor **1a**, these amines yield the corresponding imines, which exist completely as the tautomeric enamines **3a**–**p**; these enamines are isolable, after chromatography, in good to excellent yields (85–95%).

In a primary screening the enaminoesters **3a**–**p** were each converted in the presence of catalytic amounts of 14 different metal salts **5a**–**n**[14] with MVK (**4**) in CH_2Cl_2. If a positive effect was observed relative to the noncatalyzed reaction, with regard to the selectivity of the formation of Michael product **6a**, we started to optimize the reaction parameters. At this first stage of the screening, we did not pay attention to the

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Table 1. Selected results for the screening of enaminoesters **3** with MVK (**4**) in the presence of different metal salts **5**.[a]

Enamine	*ee* (**6a**) [%][b] without metal salt	Metal salt (mol%)	*ee* (**6a**)[b] [%]	Metal salt (mol%)	*ee* (**6a**)[b] [%]
3c	28	$Cu(OAc)_2 \cdot H_2O$ (10)	59	$SnCl_2$ (5)	43
3d	47	$Cu(OAc)_2 \cdot H_2O$ (5)	57	$FeCl_3$ (5)	59
3e	53	$Cu(OAc)_2 \cdot H_2O$ (10)	73	$FeCl_3$ (5)	50
3g	78	$Cu(OAc)_2 \cdot H_2O$ (20)	86	$Cu(OTf)_2$[c] (10)	68
3h	72	$Cu(OAc)_2 \cdot H_2O$ (5)	76	$FeCl_3$ (5)	77
3i	66	$Cu(OAc)_2 \cdot H_2O$ (20)	86	$FeCl_3 \cdot 6H_2O$ (10)	73
3l	33	$Cu(OAc)_2 \cdot H_2O$ (5)	20	$SnCl_2$ (15)	50
3m	29	$NiCl_2$ (5)	37	$SnCl_2$ (17.5)	35
3o	20	$Ni(OAc)_2 \cdot 4\,H_2O$ (5)	23	$FeCl_3$ (5)	21

[a] Reaction conditions: Scale = approximately 0.20 mmol of **3**; **3**:**4** = 1:2; solvent = CH_2Cl_2. [b] The *ee* value of **6a** was determined by GC on a chiral phase.[15] The yields were not determined. [c] Tf = F_3CSO_2.

yield. Selected results are given in Table 1. Auxiliaries derived from valine and iso- or *tert*-leucine with an additional amide function (**2a**–**i**), when attached to the Michael donor, induced selectivities up to 78% *ee* even without any metal salt. In every case the *R* isomer was found to be the major enantiomer.[8] When $Cu(OAc)_2 \cdot H_2O$ was applied as the catalyst, the *ee* values were clearly improved by about 20%. Auxiliaries with a thioether or tertiary amino function did not show promising results and, for this reason, were not considered for further optimizations.

Improvement in selectivity was also achieved by variation of the solvent: With acetone as the solvent the enantioselectivity for the copper(II) catalysis was dramatically raised. Greater than 95% *ee* values were obtained with the enaminoesters **3a**, **c**, **d**, **f**, **g**, and **i** (Table 2). In particular, when

Table 2. Asymmetric Michael reactions of enaminoesters **3** with MVK (**4**) in the presence of $Cu(OAc)_2 \cdot H_2O$ (**5a**) in acetone.[a]

Enamine	*ee* (**6a**) [%][b] amount of **5a** [mol%]				
	0	2.5	5	10	20
3a	57	98	98	98	98
3b	65	83	84	85	85
3c	55	93	95	94	92
3d	55	95	97	98	92
3f	76	93	97	90	93
3g	85	96	96	97	99
3i	70	91	92	92	91

[a] Reaction conditions: Scale = approximately 0.20 mmol of **3**; **3**:**4** = 1:2; solvent = acetone. [b] For enantioselectivities of greater than 95% the *ee* values were additionally checked after derivatization to **7a**.[15]

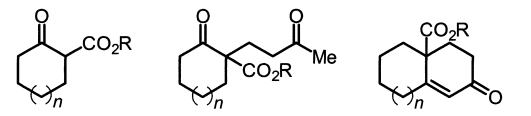
compounds **3a** and **3d** were used with 2.5 or 10 mol% of catalyst, selectivities of up to 98% *ee* were achieved. An increase to 99% *ee* resulted when compound **3g** was used in the presence of 20 mol% $Cu(OAc)_2 \cdot H_2O$. With these results, the protocol presented here is the most selective method known so far for the stereoselective generation of quaternary carbon centers by Michael reactions of β-oxoesters with MVK. However, only the auxiliaries derived from valine and iso- or *tert*-leucine show such high selectivities. The yields are dependent upon the reaction time and the amount of catalyst applied. The use of 2.5 mol% of catalyst gives 65–75% yield after 12–14 h. If more catalyst is employed, the yields rise to 80–90%. Without any catalyst the yield is less than 15% after 12–14 h. We were further interested in whether our method could be transferred to cyclic Michael donors with different ring sizes. As shown in Table 3, the Michael product **6b** can be prepared with an *ee* value of greater than 98% from the five-membered ring β-oxoester **1b** attached to auxiliary **2g**.[15] The seven-membered ring compound **1c** can be converted into

Table 3. Variation of the Michael donor **1** in acetone.

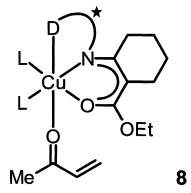
Michael donor	Auxiliary	Catalyst [mol%]	Product	*ee* [%]	Yield [%]
1b	**2g**	5	**6b**[a]	≥ 98	40
1c	**2g**	10	**6c**	74[b]	84

[a] *R* enantiomer.[8] [b] The *ee* of **6c** was determined after derivatization to **7b**.[15]

product **6c** in 74% *ee* by use of the same auxiliary **2g** (*ee* value determined after derivatization to compound **7b**).[15]



1b, *n* = 0, R = Et; **1c**, *n* = 2, R = Me; **6b**, *n* = 0, R = Et; **6c**, *n* = 2, R = Me; **7a**, *n* = 1, R = Et; **7b**, *n* = 2, R = Me



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Regarding the mechanism of the reaction we can only speculate at the moment. However, we suppose that this Cu-catalyzed variant of an auxiliary-mediated Michael reaction does not proceed via a cyclic transition state as proposed by d'Angelo and co-workers,[6] but instead through an intermediate **8**, in which the enamine **3** coordinates as a tridentate ligand to the copper center and, thereby, effects a diastereofacial differentiation. At the same time the enone is activated by coordination to the metal center.[8]

The copper-catalyzed auxiliary-mediated Michael reaction of cyclic β-oxoesters with MVK introduced herein allows, for the first time, the construction of quaternary stereocenters in 80–90% yield with up to 99% *ee*. The reaction proceeds at ambient temperature and under mild conditions. Exclusion of air or moisture is not necessary. As chiral auxiliaries α-amino acid amides, which are readily available by standard transformations from α-amino acids, are applied; they are almost quantitatively recoverable after the reaction.

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Experimental Section

3g (representative procedure): A mixture of (*S*)-*tert*-leucine dimethylamide (**2g**; 696 mg, 4.40 mmol), oxoester **1a** (749 mg, 4.40 mmol), and molecular sieves (4 Å, 2.5 g) in toluene (6 mL) under nitrogen was treated with a catalytic amount of concentrated HCl. After stirring for 14 h at 60 °C, the reaction mixture was filtered and the residue washed with CH_2Cl_2. All volatile materials were removed in vacuo and the residue was chromatographed on Al_2O_3 90 (Activity II–III; eluent = methyl *tert*-butylether/petroleum ether 3/1; $R_f = 0.45$) to yield **3g** as a colorless solid (1.17 g, 3.78 mmol, 86 %). m.p. 104 °C; $[\alpha]_D^{20} = +194$ ($c = 5.8$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$ (s, 9H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.47–1.58 (m, 2H), 1.58–1.67 (m, 2H), 1.99–2.09 (m, 1H), 2.22–2.34 (m, 3H), 2.97 (s, 3H), 3.11 (s, 3H), 4.09–4.20 (m, 2H), 4.24 (d, $J = 9.9$ Hz, 1H), 9.45 (d, $J = 9.8$ Hz, 1H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): $\delta = 14.61$ (CH_3), 22.43 (CH_2), 22.55 (CH_2), 23.97 (CH_2), 26.66 (CH_3), 26.76 (CH_2), 35.74 (CH_3), 35.96 (C), 37.90 (CH_3), 57.75 (CH), 58.72 (CH_2), 91.27 (C), 156.47 (C), 170.41 (C=O), 171.67 (C=O); HR MS (EI, 70 eV): calcd: 310.2256, found: 310.2249; elemental analysis (%): calcd for $C_{17}H_{30}N_2O_3$ (310.44): C 65.77, H 9.74, N 9.02; found: C 65.94, H 9.76, N 9.16.

Copper(II)-catalyzed Michael reaction of **3a** (representative procedure): Enaminoester **3a** (0.216 mmol, 70.1 mg) and $Cu(OAc)_2 \cdot H_2O$ (**5a**; 0.0054 mmol, 1.1 mg) were stirred in acetone (1 mL) at 23 °C for 1 h. MVK (**4**; 0.43 mmol, 30 mg) was added and the mixture was stirred for additional 12–14 h at 23 °C. All volatile materials were removed in vacuo and the residue was treated with 2 N HCl. The mixture was stirred vigorously for 4–5 h and subsequently extracted with methyl *tert*-butylether.[16] After washing (saturated aqueous $NaHCO_3$) und drying ($MgSO_4$) of the combined extracts, the solvent was evaporated and the residue was chromatographed on SiO_2 (methyl *tert*-butylether/petroleum ether 1/2, $R_f = 0.19$). Compound **6a** (0.186 mmol, 44.6 mg, 86 %) was obtained as a colorless oil. The *ee* value of 98 % was determined by GC with a chiral column after derivatization to compound **7a**.[15]

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[12] Syntheses of auxiliaries **2a**–**j** were accomplished in three steps from the appropriate α-amino acids: a) Boc_2O, DMAP (3 mol %), H_2O/MeOH 1/1, 70–80 %; b) DCC, HNR'_2, CH_2Cl_2, 65–85 %; c) CF_3CO_2H, CH_2Cl_2, 90–99 %. Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, DCC = dicyclohexylcarbodiimide.

[13] Syntheses of auxiliaries **2m**–**p** were accomplished in four steps from the appropriate amino alcohols: a) Boc_2O, CH_2Cl_2, quantitative; b) TosCl, pyridine, 65–90 %; c) for **2m**, **n**: NaSEt, DMF, 90–95 %; for **2o**, **p**: $HNMe_2$, pyridine, 75–95 %; d) CF_3CO_2H, CH_2Cl_2, 90–99 %. Tos = *p*-$H_3CC_6H_4SO_2$.

[14] Applied metal salts: $Cu(OAc)_2 \cdot H_2O$ (**5a**), $Cu(OTf)_2$ (**5b**), $FeCl_3$ (**5c**), $FeCl_3 \cdot 6\,H_2O$ (**5d**), $NiCl_2$ (**5e**), $Ni(OAc)_2 \cdot 4H_2O$ (**5f**), $SnCl_2$ (**5g**), AgOAc (**5h**), $CoCl_2 \cdot 6H_2O$ (**5i**), $CrCl_3 \cdot 6H_2O$ (**5j**), $MgBr_2$ (**5k**), $Pb(OAc)_2 \cdot 3H_2O$ (**5l**), $ZnBr_2$ (**5m**), $ZnCl_2$ (**5n**). Tf = F_3CSO_2.

[15] Details about GC analysis and derivatization procedures have recently been reported by us.[8]

[16] Auxiliary **2** can be almost quantitatively recovered from the aqueous layer after basic workup.

Detection of a 2,3-Aminomutase in the Mushroom *Cortinarius violaceus***

Peter Spiteller, Matthias Rüth, Franz von Nussbaum, and Wolfgang Steglich*

Recently, we discovered the new natural β-amino acid (*R*)-3,4-dihydroxy-β-phenylalanine ((*R*)-β-dopa, (*R*)-**3**) in the mushroom *Cortinarius violaceus*.[1] (*R*)-**3** is present in the mushroom as the iron(III)–catechol complex, which gives the fruit bodies their blue-purple color.

In this communication we report on the biosynthesis of (*R*)-β-dopa. For this purpose, suitable precursors were applied to young fruit bodies of *C. violaceus*, which were then harvested 5 to 7 days later. All mushrooms showed normal growth and became double their original size. After extraction of the fruit bodies with methanol, the amino acids were isolated by ion exchange chromatography and further investigated by GC/MS as their trimethylsilyl derivatives. The incorporation of ^{13}C-labeled precursors was determined by NMR spectroscopy.

After feeding with *rac*-3-fluorotyrosine, we were able to detect the formation of 5-fluoro-β-dopa as well as traces of 3-fluoro-β-tyrosine (Table 1, entry 1).[2] This proves that tyrosine (**1**) is the biosynthetic precursor of β-dopa (**3**). This result is confirmed by the successful conversion of *rac*-[3′-

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