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Asymmetric Michael addition using *N*-cinnamoyl- and *N*-crotonyl-*trans*-hexahydrobenzoxazolidin-2-ones

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Abstract—Preparation of *N*-cinnamoyl- and *N*-crotonyl-oxazolidin-2-ones **2** and **3** or ***ent*-2** and ***ent*-3** from (4*S*,5*S*)- and (4*R*,5*R*)-*trans*-hexahydrobenzoxazolidin-2-ones **1** or ***ent*-1** are reported. Stereoselective copper promoted conjugated additions of Grignard reagents to chiral *N*-enoyl amides **2** and **3** or ***ent*-2** and ***ent*-3** in the presence of Zn(II) salts afforded the 1,4-addition products **4**–**11** and the corresponding enantiomers.

1. Introduction

Michael addition reactions represent one of the most important carbon–carbon bond forming reactions in modern synthetic organic chemistry.[1] The asymmetric 1,4-addition reactions of organometallics into α,β-unsaturated esters and amides have been demonstrated to provide products in high chemical and stereochemical purity, and represent a valuable transformation to achieve chiral β-substituted carboxylic acids.[2]

Organocopper reagents are among the most versatile reagents available for conjugate addition reactions.[3] Chiral catalysts[4] and chiral auxiliaries[5] have been used efficiently for copper promoted asymmetric conjugated additions of Grignard reagents.

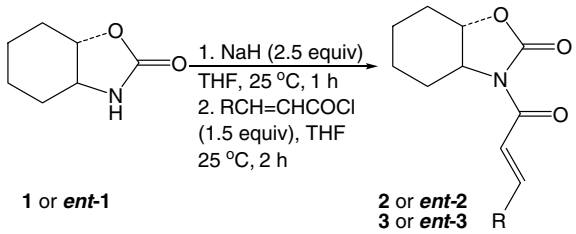
Recently, we reported a convenient procedure for the preparation of (4*S*,5*S*)- and (4*R*,5*R*)-*trans*-hexahydrobenzoxazolidin-2-ones **1** and ***ent*-1** from inexpensive cyclohexene oxide and (*S*)-α-phenylethylamine.[6,7]

We now report the preparation of *N*-cinnamoyl- and *N*-crotonyl-amides **2** and **3** or ***ent*-2** and ***ent*-3**,[8] and the asymmetric Michael addition reactions in the presence of Grignard reagents, CuBr–DMS (dimethyl sulfide), DMS, and Zn(II) salts.

2. Results and discussion

The preparation of *N*-enoyl-oxazolidinones **2** and **3** or ***ent*-2** and ***ent*-3** (Table 1) was performed by deprotonation of the chiral auxiliaries **1** and ***ent*-1** with NaH (2.5 equiv) in THF at 25 °C for 1 h.[8] The acylating agents (1.5 equiv, cinnamoyl- and crotonyl chloride) were slowly added at 25 °C and the reaction mixture was stirred for 2 h. The crude products were purified by column chromatography on silica gel affording the *N*-enoyl-amides **2** and **3** or ***ent*-2** and ***ent*-3** in 80–81% yield (Table 1).

Table 1. N-Acylation of *trans*-oxazolidin-2-ones **1** and ***ent*-1**



Entry	Oxazolidinone	R	Product	Yield (%)[a]	$[\alpha]_D$[b]
1	**1**	Ph	**2**	81	+11.0
2	**1**	CH_3	**3**	81	+7.4
3	***ent*-1**	Ph	***ent*-2**	80	−10.9
4	***ent*-1**	CH_3	***ent*-3**	80	−7.0

[a] Yields were measured after purification by column chromatography on silica gel [hexanes–EtOAc (6:1)].
[b] Optical rotations were measured in *c* 1.0, $CHCl_3$.

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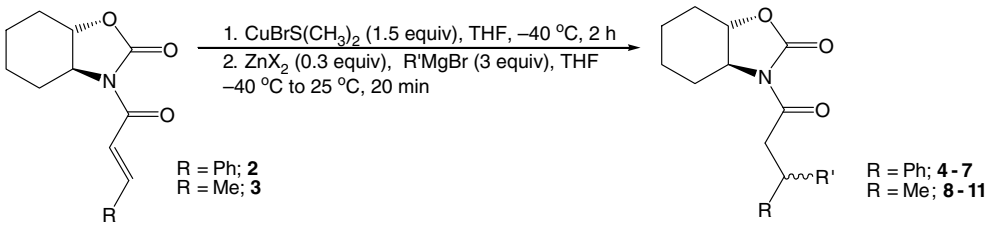
Table 2. 1,4-Addition to (4*S*,5*S*,2′*E*)-*N*-(cinnamoyl)- and *N*-(crotonyl)-oxazolidin-2-ones **2** and **3**



Entry	Substrate	R′	ZnX_2	Major product[a]	Yield (%)[b]	dr (*R*:*S*)[c]
1	**2**	Me	[d]	(4*S*,5*S*,3′*R*)-**4**	40	78:22
2	**2**	Me	ZnI_2	(4*S*,5*S*,3′*R*)-**4**[e]	75	91:9
3	**2**	Me	$ZnBr_2$	(4*S*,5*S*,3′*R*)-**4**	72	87:13
4	**2**	Me	$ZnCl_2$	(4*S*,5*S*,3′*R*)-**4**	72	79:19
5	**2**	Me	$Zn(CF_3SO_3)_2$	(4*S*,5*S*,3′*R*)-**4**	70	85:14
6	**2**	Et	ZnI_2	(4*S*,5*S*,3′*R*)-**5**	81	90:10
7	**2**	*n*-Pr	ZnI_2	(4*S*,5*S*,3′*R*)-**6**	80	86:14
8	**2**	*n*-Bu	ZnI_2	(4*S*,5*S*,3′*R*)-**7**	76	84:16
9	**3**	Ph	[d]	(4*S*,5*S*,3′*S*)-**8**	44	41:59
10	**3**	Ph	ZnI_2	(4*S*,5*S*,3′*S*)-**8**[e]	75	25:75
11	**3**	Et	ZnI_2	(4*S*,5*S*,3′*S*)-**9**	79	12:88
12	**3**	*n*-Pr	ZnI_2	(4*S*,5*S*,3′*S*)-**10**	76	16:84
13	**3**	*n*-Bu	ZnI_2	(4*S*,5*S*,3′*S*)-**11**	78	19:81

[a] Configuration of major products were assigned by chemical correlation with the corresponding carboxylic acids, by optical rotation and HPLC analysis with a Chiralcel OD column, see Ref. 9.
[b] Yields were measured after purification by column chromatography on silica gel [hexanes–EtOAc (5:1)].
[c] Diastereoisomeric ratios were measured from ^{1}H NMR spectra of crude products.
[d] Conjugated additions were performed in the absence of zinc salt.
[e] Assignments of absolute configuration were obtained by X-ray diffraction crystallography from suitable single crystals.

First, *N*-cinnamoyl-amide **2** (1 equiv) was added to CuBr–DMS complex (1.5 equiv), followed by the addition of MeMgBr (3 equiv) in THF at −40 °C, affording (4*S*,5*S*,3′*R*)-**4** as the major diastereoisomer (Table 2, entry 1). The 1,4-addition reaction gave low yield (40%) and moderate diastereoisomeric ratio (78:22). Then, improved yields (up to 75%) and diastereoisomeric ratios (up to 91:9) were obtained in the presence of zinc salts (0.3 equiv): -chloride, -bromide, -iodide, and -triflate (Table 2, entries 2–5). The best diastereoisomeric ratio was observed by adding ZnI_2 (Table 2, entry 2). So, we proceeded to perform the conjugated addition of other copper-promoted Grignard reagents to *N*-cinnamoyl-oxazolidinone **2** employing Et-, *n*-Pr-, and *n*-BuMgBr in the presence of ZnI_2. The diastereoisomeric ratios were measured on clearly resolved ^{1}H NMR signals of the crude reactions (Table 2, entries 7–9). The crude products were purified by column chromatography on silica gel affording the conjugated addition compounds **5**–**7** in good yields after column chromatography (76–81%).

The same methodology for the conjugated addition of copper-promoted Grignard reagent was performed with *N*-crotonyl amide **3** in the presence of PhMgBr. By the same token, without ZnI_2 afforded (4*S*,5*S*,3′*S*)-**8** as the major diastereoisomer in low yield and poor diastereoisomeric ratio (Table 2, entry 9, 44% yield, dr 41:59). Addition of ZnI_2 to the reaction mixture increased both yield and diastereoisomeric ratio (Table 2, entry 10, 75% yield, 25:75). So, we proceeded to perform the conjugated addition to *N*-crotonyl-hexahydrobenzoxazolidin-2-one **3** of organocopper reagents formed with Et-, *n*-Pr-, and *n*-BuMgBr in the presence of ZnI_2. The 1,4-addition reactions afforded **9**–**11** in good yields after column chromatography purification (Table 2, entries 11–13, 76–79% yield, and up to 12:88 dr).

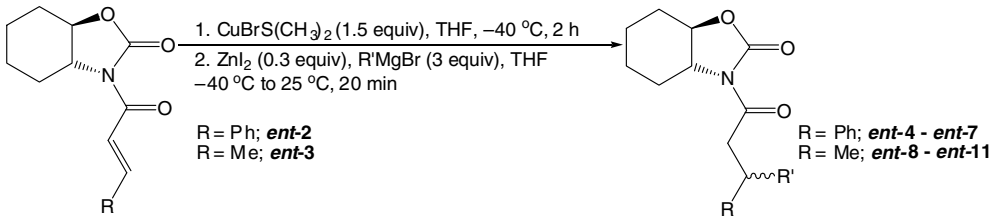
Finally, we performed the conjugated addition reactions to the enantiomers (4*R*,5*R*,2′*E*)-*N*-cinnamoyl- and *N*-crotonyl-oxazolidin-2-ones ***ent*-2** and ***ent*-3** using the protocol already described. The Michael reactions afforded ***ent*-4**–***ent*-11** (Table 3, entries 1–8, 74–81% yield, and up to 10:90 dr).

Chemical correlation by basic hydrolysis of *N*-cinnamoyl- and *N*-crotonyl-1,4-addition products **4**–**11** and ***ent*-4**–***ent*-11** afforded the corresponding 3-phenyl- and 3-methyl-carboxylic acids, which were previously reported in the literature, and the oxazolidinones **1** and ***ent*-1** were recovered (81–90% yield).[9]

The products **4** and **8** (Table 2, entries 2 and 10) were recrystallized from hexanes–isopropanol (10:1). The absolute configuration at the new stereogenic center in both compounds were assigned by X-ray diffraction analysis from suitable single crystals.[10,11]

As is well known, bulkier groups at position 4 of oxazolidin-2-ones induced higher stereoselectivities on the β-position of the double bond, that is: phenyl > *tert*-butyl > isopropyl ≫ benzyl.[3] We compared the diastereoselectivities obtained with our oxazolidinones **2** and **3** in the absence of ZnI_2 with other chiral auxiliaries, and we observed that the results were only slightly better than those reported with *N*-enoyl-4-benzyl-2-oxazolidi-

Table 3. 1,4-Addition to (4*R*,5*R*,2′*E*)-*N*-(cinnamoyl)- and *N*-(crotonyl)-oxazolidin-2-ones ***ent*-2** and ***ent*-3**



Entry	Substrate	R′	Major product[a]	Yield (%)[b]	dr (*R*:*S*)[c]
1	***ent*-2**	Me	(4*R*,5*R*,3′*S*)-***ent*-4**	75	10:90
2	***ent*-2**	Et	(4*R*,5*R*,3′*S*)-***ent*-5**	81	12:88
3	***ent*-2**	*n*-Pr	(4*R*,5*R*,3′*S*)-***ent*-6**	79	15:85
4	***ent*-2**	*n*-Bu	(4*R*,5*R*,3′*S*)-***ent*-7**	77	18:82
5	***ent*-3**	Ph	(4*R*,5*R*,3′*R*)-***ent*-8**	74	74:26
6	***ent*-3**	Et	(4*R*,5*R*,3′*R*)-***ent*-9**	78	85:15
7	***ent*-3**	*n*-Pr	(4*R*,5*R*,3′*R*)-***ent*-10**	78	80:20
8	***ent*-3**	*n*-Bu	(4*R*,5*R*,3′*R*)-***ent*-11**	75	77:23

[a] Configuration of major products were assigned by chemical correlation with the corresponding carboxylic acids, by optical rotation and HPLC analysis with a Chiralcel OD column, see Ref. 9.
[b] Yields were measured after purification by column chromatography on silica gel [hexanes–EtOAc (5:1)].
[c] Diastereoisomeric ratios were measured from ^{1}H NMR spectra of crude products.

nones.[3b,f] However, in the presence of ZnI_2, we observed a substantial improvement on diastereoselectivities, which were similar to those reported with *N*-enoyl-4-isopropyl-2-oxazolidinones.[3e] We surmise that it is due to the chelation of Zn(II) with the carbonyl groups, so the precomplexed Zn(II)/oxazolidinones seemed to react in a *syn-s-cis* conformation.

The study of stereoselective conjugated addition reactions is an ongoing project in our laboratory. Preliminary results showed that Michael addition reactions to *trans*-*N*-cinnamoyl- and *N*-crotonyloxazolidin-2-ones **2** and **3** or ***ent*-2** and ***ent*-3** in the presence of ZnI_2 (0.3 equiv) proceed with good yields (75–81%) and good diastereoisomeric ratios (up to 91:9). The configuration of the new stereogenic center is based on the chiral auxiliaries **1** or ***ent*-1** employed.

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10. (4*S*,5*S*,3′*R*)-3-(3′-Phenylbutanoyl)-hexahydrobenzoxazolidin-2-one **4**: The product was recrystallized from hexane: isopropanol (10:1) affording the major diastereoisomer as colorless crystals; mp 72–74 °C, $[\alpha]_D$ +13.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ: 7.0–7.28 (m, 5H); 3.61 (td, 1H, $J = 11$, $J = 4$), 3.44 (td, 1H, $J = 11$, $J = 4$), 3.37 (dd, 1H, $J = 16$, $J = 6$), 3.34 (m, 1H), 3.00 (dd, 1H, $J = 16$, $J = 6$), 2.70 (m, 1H), 2.65 (m, 1H), 1.81 (m, 2H), 1.57 (qd, 1H, $J = 12$, $J = 4$), 1.34 (d, 3H, $J = 8$), 1.28 (m, 1H), 1.11 (qd, 2H, $J = 12$, $J = 4$); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ: 172.4, 155.2, 144.8, 128.4, 128.3, 127.2, 81.34, 63.0, 44.4, 36.9, 28.5, 28.4, 23.6, 23.5, 22.0; IR (cm^{-1}): 2866, 2360, 1782, 1689, 1311, 1033, 759. MS (*m*/*z*): 287 (M^+), 272, 183, 142, 118, 105; HRMS-FAB+ *m*/*z* found 288.1604 $[(M+H)^+$ calcd 288.1600 for $C_{17}H_{21}NO_3$]. X-ray structure: Colorless plate, $0.60 \times 0.24 \times 0.16$ mm^3, $C_{17}H_{21}NO_3$. Monoclinic, $P2_1$, $a = 10.5810(15)$, $b = 5.4279(14)$, $c = 13.743(2)$ Å, $\beta = 95.936(11)°$, $Z = 2$, $\rho_{calc} = 1.216$ g cm^{-3}. A set of 3749 reflections was collected using Mo-K_α radiation ($\lambda = 0.71073$ Å), corresponding to $2\theta_{max} = 52.6°$, and 1997 independent reflections ($R_{int} = 0.050$) were used for the refinement of 191 parameters, without neither restraints nor constraints (SHELXTL 5.10 package). H atoms were placed in idealized positions and refined using a riding model. Final *R* indices: $R_1 = 0.052$ for 1442 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.151$ for all data. The absolute configuration for the chiral centers was assigned assuming that the configuration of the chiral starting material was unchanged during the synthesis. CCDC deposition number: 278745. Structure factors and raw files are available on request to authors.
11. (4*S*,5*S*,3′*S*)-3-(3′-Phenylbutanoyl)-hexahydrobenzoxazolidin-2-one **8**: The product was recrystallized from hexane: isopropanol (10:1) affording the major diastereoisomer as colorless crystals; mp 74–78 °C, $[\alpha]_D$ −12.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ: 7.17–7.24 (m, 5H), 3.78 (td, 1H, $J = 11$, $J = 4$), 3.60 (td, 1H, $J = 11$, $J = 4$), 3.36 (dd, 1H, $J = 16$, $J = 6$), 3.34 (m, 1H), 3.00 (dd, 1H, $J = 16$, $J = 6$), 2.67 (m, 1H), 2.16 (m, 1H), 1.78 (m, 1H), 1.57 (qd, 2H, $J = 12$, $J = 4$), 1.30 (d, 3H, $J = 8$), 1.28 (m, 2H), 0.89 (qd, 1H, $J = 12$, $J = 4$), ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ: 174.2, 154.7, 145.7, 128.4, 127.1, 126.4, 81.3, 63.0, 44.4, 36.8, 28.5, 28.4, 23.7, 23.5, 22.4; IR (cm^{-1}): 2866, 2360, 1782, 1689, 1311, 1033, 759; MS (*m*/*z*): 287 (M^+), 272, 183, 142, 118, 105; HRMS-FAB+ *m*/*z* found 288.1600 $[(M+H)^+$ calcd 288.1599 for $C_{17}H_{21}NO_3$]. X-ray structure: Colorless needle, $0.60 \times 0.14 \times 0.14$ mm^3, $C_{17}H_{21}NO_3$. Monoclinic, $P2_1$, $a = 11.1885(14)$, $b = 5.4166(6)$, $c = 13.1885(15)$ Å, $\beta = 108.267(9)°$, $Z = 2$, $\rho_{calc} = 1.257$ g cm^{-3}. A set of 3033 reflections was collected using Mo-K_α radiation ($\lambda = 0.71073$ Å), corresponding to $2\theta_{max} = 52.5°$, and 1706 independent reflections ($R_{int} = 0.029$) were used for the refinement of 191 parameters, without neither restraints nor constraints (SHELXTL 5.10 package). H atoms were placed in idealized positions and refined using a riding model. Final *R* indices: $R_1 = 0.035$ for 1379 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.092$ for all data. The absolute configuration for the chiral centers was assigned assuming that the configuration of the chiral starting material was unchanged during the synthesis. CCDC deposition number: 278746. Structure factors and raw files are available on request to authors.