Copper(I)-catalysed asymmetric conjugate addition of organozirconocenes to *N*-acyl oxazolidinones

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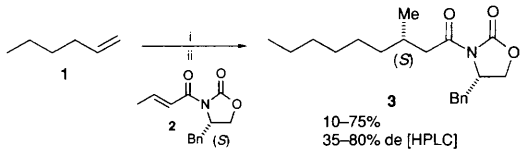
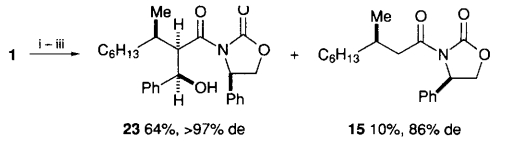
Copper(I)-catalysed conjugate addition of *in situ* prepared alkylzirconocenes to α,β-unsaturated *N*-acyl oxazolidinones followed by enolate trapping provided up to three new stereocentres with excellent diastereoselectivities.

The 1,4-addition of organometallic compounds is an important method for C–C bond formation in organic synthesis.[1] Asymmetric versions with achiral enones include the use of chiral heterocuprates or chiral ligands.[2,3] In the addition of achiral organocopper reagents to chiral alkenoate derivatives, the use of chiral esters and imides,[2,4] specifically Oppolzer's sultam,[5] Evans' oxazolidinone[6] and Koga's butyrolactam,[7] have provided high diastereoselectivities. We have recently reported the copper-catalysed conjugate addition of alkylzirconocenes to enones.[8] Alkylzirconocenes are readily available by *in situ* hydrozirconation of alkenes, and a broad range of functional groups including silyl esters can be tolerated in this reaction.[9] Therefore, this protocol represents a useful extension of standard organocuprate additions.[10] We now report the first asymmetric version of the copper-catalysed 1,4-addition of organozirconocenes.

Treatment of hex-1-ene **1** with $(C_5H_5)_2Zr(H)Cl$ (Schwartz reagent) followed by addition of the crotyl derivative of benzyloxazolidinone **2**[11] and 15 mol% of $CuBr{\cdot}SMe_2$ complex in three portions at room temp. provided the 1,4-addition product **3** in 10–75% yield depending on the reaction solvent. The presence of a Lewis acid was crucial for achieving high diastereoselectivities and optimal chemical yield (73%) and highest de (80%) was achieved by a combination of THF and 1 equiv. of BF_3–Et_2O (Scheme 1). Even under these optimized conditions, however, the diastereoselectivity dropped to unacceptable levels (<60%) when secondary zirconocenes were used, or when the alkene contained Lewis-basic functional groups (Table 1). A change of the chiral auxiliary to the valine-derived isopropyloxazolidinone **10** led to a slight increase of the %de in the addition of hex-1-ene, but similarly disappointing results were obtained with secondary or functionalized organozirconocenes. The use of the Oppolzer sultam **12** led to even more drastic losses in diastereoselectivity as well as chemical yield in the conjugate addition reaction. Hruby and co-workers have used a phenylglycine-derived oxazolidinone as auxiliary in the copper-catalysed conjugate addition of aryl and methyl Grignard reagents.[6a] In our *in situ* hydrozirconation–conjugate addition sequence with hex-1-ene, the use of crotonate **14** resulted indeed in the formation of the addition product **15** in a superior 90% de and in acceptable 64% chemical yield. More importantly, the cyclohexyl-substituted **16** was isolated in 74% yield and in 84% de, and even the ester **17** was readily formed in 82% de from the corresponding alkene **6**. The silyl ether **19** was prepared in 88% de, and the use of a cinnamate in place of the crotonate resulted in the formation of the β-aryl heptanoates **21** and **22** as 97:3 and 95:5 ratios of diastereoisomers, respectively.‡



Scheme 1 *Reagents and conditions*: i, $(C_5H_5)_2Zr(H)Cl$, solvent (THF, DME, dioxane, CH_2Cl_2, oxetane); ii, $CuBr{\cdot}SMe_2$ (3 × 5 mol%), 2 h, 21 °C, Lewis acid [BF_3, $ZnCl_2$ $Al(OEt)_3$, Bu_2BOTf, $Ti(OPr^i)_4$, $TiCl_4$]

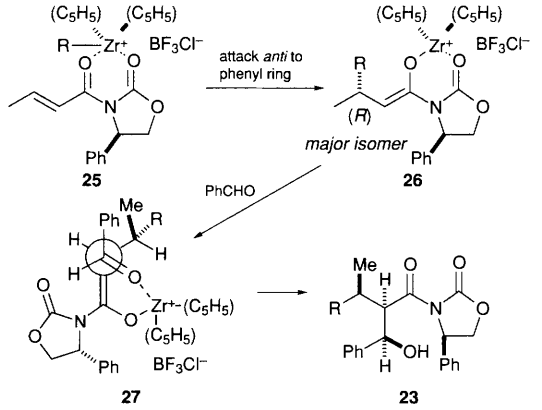


Scheme 2 *Reagents and conditions*: i, $(C_5H_5)_2Zr(H)Cl$, THF; ii, **14**, $CuBrSMe_2$ (3 × 5 mol%), 10 min, 40 °C, $BF_3{\cdot}OEt_2$ (1.0 equiv.); iii, PhCHO, 2 h, −78 °C

One of the advantages of using Evans' oxazolidinone is the possibility of effecting a conjugate addition–enolate trapping sequence that benefits from the high level of asymmetric induction generally observed for aldol reactions with this class of auxiliaries.[13] Indeed, addition of 1 equiv. of benzaldehyde to the conjugate addition mixture of hex-1-ene and crotonate **14** provided the *syn*-aldol product **23** in 64% yield as a single diastereoisomer (Scheme 2).[14] Three contiguous stereocentres were established in a single one-pot reaction in this reaction.§ In addition to the aldol product, the proton quenching side product **15** was isolated in 10% yield.

The ratio of **23** to **15** depended considerably on the time interval between the addition of oxazolidinone **14** and aldehyde to the reaction mixture. If the reaction was stirred for 6 h at room temp. before benzaldehyde was added, only 18% of **23** and 63% of **15** was isolated. This is indicative of a competitive enolate deactivation under the reaction conditions.

The presence of the hard Lewis acid BF_3–Et_2O was again crucial to achieve satisfactory yields in the aldol process, but its exact role remains unknown. A proposal for the transition state of the conjugate addition and the ensuing aldol reaction is given in Scheme 3. Formation of the chelated zirconocene complex **25** is initiated by the reversible abstraction of chloride ligand by the Lewis acid,[15] and rapid copper-catalysed conjugate addition occurs *anti* to the phenyl substituent to give the major isomer **26**. Upon addition of aldehyde, the chelated, cationic zirconium

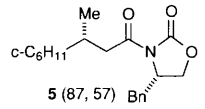
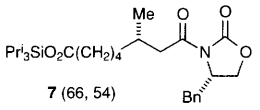
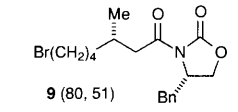
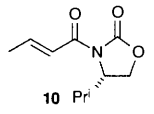
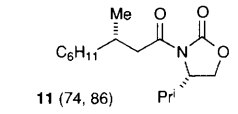
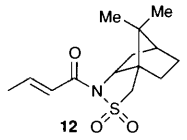
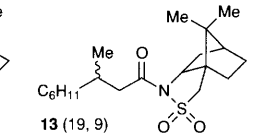
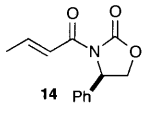
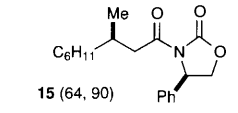
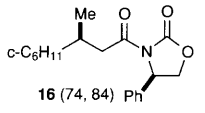
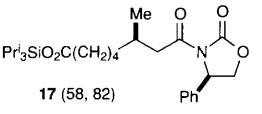
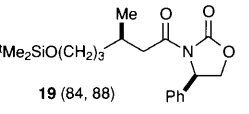
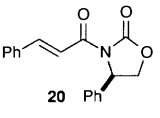
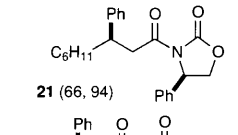
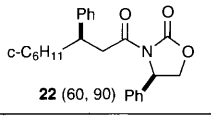


Scheme 3

complex reacts *via* a six-membered Zimmerman–Traxler transition state **27** to give the *syn*-aldol product **23**.

In summary, this communication describes the *in situ* hydrozirconation-conjugate addition sequence of alkenes to acyl oxazolidinones that provides functionalized β-branched carboxylic acids in 81–94% diastereoselectivity. Since alternative asymmetric methods have largely been limited to the introduction of unfunctionalized β-methyl and -aryl groups,[6] the copper-catalysed conjugate addition of zirconocenes represents a new synthetically useful extension of Evans' chiral auxiliaries. Conjugate addition–enolate trapping can be used to establish three consecutive chiral centres in very high (>97%) diastereoselectivity.

Table 1 Cu^{I}-catalysed asymmetric 1,4-addition reactions of *in situ* prepared alkylzirconocenes

Alkene	Enone	Product (% yield,[a] % de)
1	**2**	**3** (73, 80)
cyclohexene **4**	**2**	 **5** (87, 57)
$Pr^{i}_3SiO_2CCH_2CH_2CH=CH_2$ **6**	**2**	 **7** (66, 54)
4-bromobutene **8**	**2**	 **9** (80, 51)
1	 **10**	 **11** (74, 86)
1	 **12**	 **13** (19, 9)
1	 **14**	 **15** (64, 90)
4	**14**	 **16** (74, 84)
6	**14**	 **17** (58, 82)
$Bu^{t}Me_2SiOCH_2CH=CH_2$ **18**	**14**	 **19** (84, 88)
1	 **20**	 **21** (66, 94)
4	**20**	 **22** (60, 90)

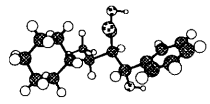
[a] Yields are based on *N*-acyl oxazolidinone and chromatographically purified product.

Footnotes

† Diastereoselectivities were determined by ^1H NMR and HPLC on SiO_2. The C(3)-stereochemistry of **3** was determined by cleavage of the chiral auxiliary and comparison of the $[\alpha]_D$ of the resulting acid with the reference reported by Meyers *et al.* (ref. 12). The absolute stereochemistry of other products was assigned by analogy with **3**.

‡ A typical procedure is as follows: a solution of 68 mg (0.82 mmol) of hex-1-ene **1** in 1 ml of THF was treated at 21 °C with 159 mg (0.62 mmol) of $(C_5H_5)_2Zr(H)Cl$. The mixture was stirred at 21 °C until a homogenous solution formed. After another 5 min, 50 μl (0.41 mmol) of $BF_3{\cdot}OEt_2$, 100 mg (0.41 mmol) of **14** and 4.2 mg (0.02 mmol) of $CuBr{\cdot}SMe_2$ were added. The dark green solution was stirred at 21 °C for 2 h with two additional portions of 4.2 mg of $CuBr{\cdot}SMe_2$ being added in 20 min intervals. The reaction mixture was quenched with wet Et_2O and extracted with sat. aqueous $NaHCO_3$ (2 ×). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (EtOAc–hexane, 1 : 4) to give 99 mg (73%) of **15** as a white solid: mp 45–47 °C; $[\alpha]_D$ −43.3 (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.41–7.29 (m, 5 H), 5.44 (dd, 1 H, *J* = 8.8, 3.8 Hz), 4.70 (t, 1 H, *J* = 8.8 Hz), 4.28 (dd, 1 H, *J* = 8.8, 3.7 Hz), 2.99 (dd, 1 H, *J* = 16.1, 5.3 Hz), 2.68 (dd, 1 H, *J* = 16.1, 8.6 Hz,), 2.05–1.95 (m, 1 H), 1.23 (brs, 10 H), 0.89–0.85 (m, 6 H).

§ The relative stereochemistry of **23** was assigned by analogy with the cyclohexene addition product. An X-ray analysis of the acid **24** obtained by hydrolysis of the auxiliary unambiguously established the structure of the latter compound:



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