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Vanadium (II) Promoted Diastereo- and Enantioselective Intermolecular Pinacol Cross Coupling.

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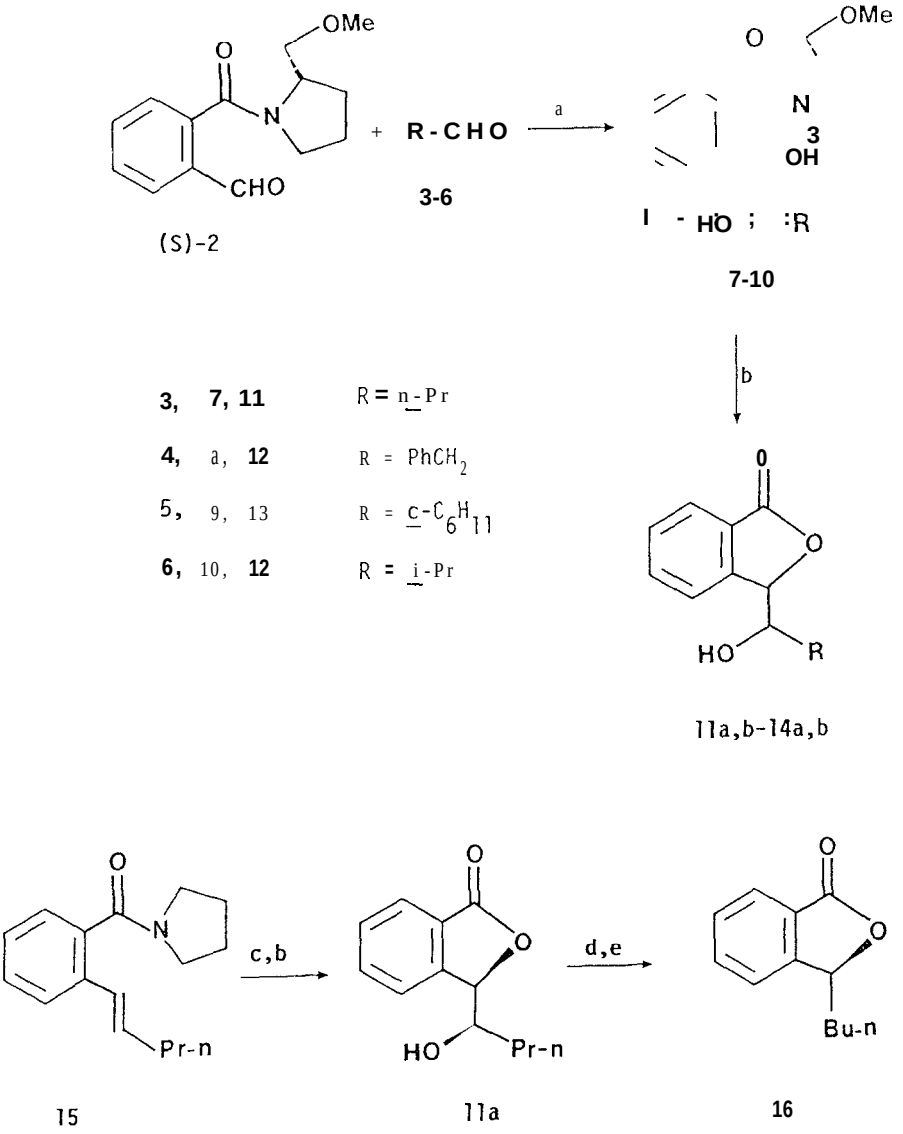
Abstract. The cross coupling reaction promoted by $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ of some aliphatic aldehydes with an aromatic aldehyde bearing a chiral auxiliary occurs in a stereocontrolled fashion to give syn 1,2- diols in diastereoisomeric ratios up to 91:9 and enantiomeric excesses up to 84%.

The ubiquitous presence of the 1,2-diol functionality in a number of biologically relevant compounds requires new methods for assembling this group with efficient control of relative and absolute stereochemistry. Among the available procedures osmylation of alkenes occupies a preminent position.[1,2]

In principle intermolecular pinacol cross coupling of aldehydes and ketones[3] represents an even simpler method, since it does not require control of the alkene configuration. Very recently Pedersen[4,5] reported an exceedingly convenient aldehyde cross coupling reaction promoted by the vanadium (II) complex $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$,[1,6] generated in situ[4] from $VCl_3(THF)_3$[7] and zinc dust. This syn-selective 1,2-diol synthesis is remarkably accelerated by an amide group in 'y-position with respect to one of the two carbonyls to be coupled, likely by intramolecular chelation.[4] We reasoned that an enantiomerically pure amide functionality could allow control of the absolute stereochemistry of the coupling process, thus greatly expanding its usefulness. We here report our preliminary results in this field.

Amide (S)-2, $[\alpha]_D^{22}$ + 113.7 (c 1.2, $CHCl_3$), prepared from phthalic anhydride and (S)-2-methoxymethylpyrrolidine[8] by standard functional group manipulation, was reacted[4] with aliphatic[9] aldehydes 3-6 in the presence of 1 to give diols 7-10. Since the combination of three stereocenters and of the hindered rotation about the amide bond hampered a secure evaluation of the stereochemical outcome of the reaciton, diols 7-10 were smoothly converted by a high yielding lactonization to mixtures of diastereoisomeric phthalides 11a,b-14a,b (Scheme).[10-13] Major isomers lla-14a were obtained by flash chromatography or crystallization in diastereoisomerically pure and optically active form as white solids.[14] Yields, isomer ratios, and enantiomeric

Scheme



Reagents: a: 1, CH_2Cl_2, RT, 15h; b: PTSA, THF, RT, 15h; c: OsO_4, acetyl dihydroquinidine, toluene, RT, 15h; d: thiocarbonyldiimidazole 1,2-dichloroethane, 80°C, 4h; e: Bu_3SnH, toluene, 110°C, 5h.

excesses (e.e.'s) of lla-14a are collected in Table.[15] As can be seen from the reported data this method can be applied to linear and branched aldehydes with similar success. Branching results in slightly increased e.e.'s, leaving the diastereoselectivity virtually unchanged. The syn relative configuration of the predominant isomer lla (and thus by analogy that of 12a-14a) was established by preparing this compound by osmylation of the E-alkene 15 in the presence of acetyl dihydroquinidine,[2] followed by lactonization (Scheme).[16] We could also determine the absolute configuration of lla by conversion into the known[17] (S)-3-butylphthalide 16, a component of the essential oil of celery, as described in the Scheme.

In conclusion, a highly diastereo- and enantioselective pinacol cross coupling reaction has been accomplished for the first time by the use of an inexpensive and practical V (II) reagent and of a chiral auxiliary. Work is in progress to evaluate limits and the potential of this method and to elucidate the origin of stereocontrol.[18] This study could also provide new insight into the mechanism of low-valent metal promoted carbonyl coupling reactions.

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Table. Synthesis of lactones 11a,b-14a,b from aldehydes 2 and 3-6 via 7-10.

R	Diol	Yield %	Lactone	Yield %	a:b ratio[a]	e.e.%[a,b]
n-Pr	7	73	11a,b	86	80:20	77[c]
$PhCH_2$	8	76	12a,b	93	91: 9	75[c]
$c\text{-}C_6H_{11}$	9	72	13a,b	77	88:12	83[c]
i-Pr	10	73	14a,b	85	89:11	84

[a] As determined by 300 MHz ^{1}H-NMR spectroscopy. E.e.'s evaluated by $Eu(hfc)_3$ shift reagent experiments carried out in conditions pre-established on racemic samples.[15] [b] Of the major isomers a. [c] These e.e.'s can be upgraded to $\geqslant 96\%$ by a single crystallization.

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7) _.E. Manzer, Inorg. Synth., 21, 135, 1982.

8) D. Enders, P. Fey, H. Kipphardt, Org. Synth., 65, 173, 1987. The (R)-enantiomer is also easily available.

9) Benzaldehyde gave mainly self-coupling products, while cinnamic aldehyde did not react.

10) All new compounds gave analytical and spectral data in agreement with the proposed structures.

11) This procedure apparently does not alter the stereoisomeric composition of 7-10. Indeed the syn:anti ratios determined by 300 MHz ^{1}H-NMR on some differently enriched samples of 7-10 by recording the spectra at 60°C agree well with those found for the diastereoisomeric mixtures of 11-14 obtained from those samples.

12) Only 5-membered lactones were obtained (I.R.: ν C=O at 1760-1770 cm^{-1}).

13) It must be noted that lactonization can allow the recovery of the chiral auxiliary.

14) 11a: $[\alpha]_D^{22}$ -30.8, m.p. 105-107°C; 12a: $[\alpha]_D^{22}$ -41.4, m.p. 123-125°C; 13a: $[\alpha]_D^{22}$ -45.0, m.p. 131-133°C; 14a: $[\alpha]_D^{22}$ -60.3, m.p. 140-141°C. All rotations are for c 0.5 solutions in $CHCl_3$.

15) Racemic samples of 11-14 required for the LSR determination of e.e.'s were prepared by the same route starting from N-(2-formyl)benzoylpyrrolidine.

16) The osmylation/lactonization protocol affords 11a with the same absolute configuration and in an e.e. (80%) very similar to that of the product obtained by cross coupling.

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18) Acyclic chiral γ-amidoaldehydes analogous to 2 gave cross coupling products with aliphatic aldehydes with better chemical yields but lower stereocontrol. These results will be reported in the future.