15 min, CuCN·2LiCl (1.0 equiv), -20 °C). Addition of dimethyl acetylenedicarboxylate (0.7 equiv, -60 °C, 2 h) gave the pure syn-carbometalation adduct **16** in 71% yield. The addition of the functionalized copper–zinc reagent **17** to propiolamide[14] (0.7 equiv; -30 to 0 °C, 19 h) provided the unsaturated amide **18** (100% *E*) in 53% yield (Scheme IV).

In conclusion, we have demonstrated that organozinc halides RZnX and the copper reagents RCu(CN)ZnI are perfectly compatible with primary or secondary amines and terminal alkynes. Under appropriate reaction conditions, the presence of amides and hydroxy groups was also possible, although synthetic applications may be more limited. Several new types of organometallic reagents such as **3**, **11**, and **15** were prepared and subsequently reacted with a broad range of electrophiles. This remarkable functional group tolerance avoids using protecting groups and should find numerous synthetic applications. Extensions of these studies are currently underway in our laboratories.

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Supplementary Material Available: Typical experimental procedures and full characterization data for all new compounds (7 pages). Ordering information is given on any current masthead page.

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Use of the Magnesium Cation in Aldol Additions. A Convenient Method for Achieving Anti-Aldol Selectivity

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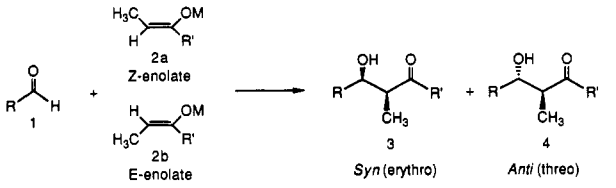
Summary: A practical and convenient procedure for achieving anti selectivity in aldol reactions which utilizes Mg(II) aldolate (or enolate) equilibrations is reported.

The aldol addition of an aldehyde (**1**) with the enolate of an ethyl ketone (**2**) gives two diastereomeric aldol products: syn (**3**) and anti (**4**) (Scheme I).[1] Over the last 20 years, this simple reaction has commanded considerable attention, resulting in its evolution from a method of limited utility to an invaluable tool in synthetic chemistry.[2] Both the geometry of the enolate and the nature of its counter cation[2,3] play important roles in controlling the diastereoselectivity of the aldol reactions. In addition, the use of enantiomeric auxiliaries[4] or enantiomeric bases[5] have

Scheme I



permitted enantiofacial selective attacks on aldehydes to favor one diastereomer over the other three possibilities.

In general, under kinetically controlled conditions, group I, II, and III metal *Z* enolates (**2a**) usually give the syn aldol products with a high degree of diastereoselection while their *E* enolates (**2b**) favor the anti product but with poorer selectivity.[2,3a,6] Recently, several research groups reported kinetically controlled procedures which result in improved anti aldol selectivity.[8] All of these results can be rationalized using some embodiment of the well-known Zimmerman/Traxler six-membered chair transition-state

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Table I. Aldol Additions Using $MgBr_2 \cdot OEt_2$ and CMDA

entry	ketone	aldehyde	anti:syn ratio (yield, %)[a] initial ratio[c] (LDA)	$MgBr_2$[c] reaction	time,[b] h	CMDA[c] reaction	time,[d] h
1	propiophenone	benzaldehyde	21:79[e]	98:2 (73)	16	92:8 (45)	1
2	propiophenone	benzaldehyde	21:79[e]	73:27 (46)[f]	16		
3	propiophenone	hexanal		87:13 (65)	16		
4	propiophenone	pentanal	29:71	89:11 (54)	5	65:35 (30)	1
5	3-pentanone	benzaldehyde	36:64	77:23 (68)	16	59:41 (82)	1
6	3-pentanone	isobutyraldehyde	69:31	91:9 (74)	5		
7	butyrophenone	isobutyraldehyde	69:31	95:5 (75)	5		
8	cyclohexanone	benzaldehyde	80:20[j]	82:18 (83)	3[g]	88:12 (98)	1
9	desoxyanisoin	benzaldehyde	56:44	93:7 (72)	16		
10	2-methyl-3-pentanone	benzaldehyde	18:82	90:10 (78)	2.5	85:15 (57)	16
11	2-methyl-3-pentanone	benzaldehyde	18:82	91:9 (82)[h]	22		
12	2-methyl-3-pentanone	hexanal	28:72[i]	81:19 (65)	16		
13	2,2-dimethyl-3-pentanone	benzaldehyde	<2:98[e]	99:1 (70)	6	>98:2 (76)	16
14	2,2-dimethyl-3-pentanone	hexanal	<2:98[i]	81:19 (50)	48		
15	α-methoxyacetophenone	benzaldehyde	40:60[i]	92:8 (86)	6	94:6 (76)	16

[a] Yields from Mg reactions are those of purified products. [b] Reaction times at room temperature after adding $MgBr_2 \cdot OEt_2$. [c] All ratios were determined by ^1H NMR and/or HPLC. [d] CMDA reactions were stirred at 0 °C for the specified times. [e] Ratios reported by Heathcock et al. (ref 3a). [f] Reaction with 0.5 molar equiv of $MgBr_2 \cdot OEt_2$. [g] Reaction conducted and quenched at −78 °C. [h] $MgBr_2 \cdot OEt_2$ was added to the Li enolate prior to the addition of aldehyde; reaction was done in ether. [i] Ratios determined by GLC of silyl derivative made with BSA/py (Tri-sel). [j] Ratio reported by Hirama et al. (ref 3e).

model.[7] By contrast, little attention had been given to methods involving syn–anti product equilibrations,[3a,9] presumably because the retro-aldol reaction competes favorably with equilibrations under most conditions. In this communication, we report a practical, facile, and convenient procedure for achieving anti selectivity in aldol reactions which utilizes Mg(II) aldolate (or enolate) equilibrations.

Two different types of magnesium-mediated aldol reactions were developed which permitted thermodynamic product control with little or no net retro-aldol reaction.[10] These are (a) the *direct* enolization of the carbonyl compound with chloromagnesium diisopropylamide (CMDA)[11] in THF, followed by reaction with the aldehyde at −70 °C and warming to room temperature, and (b) treatment of the initial aldol product(s) formed from an LDA reaction in THF with $MgBr_2 \cdot OEt_2$ at −70 °C, followed by warming to room temperature. In either case, the halomagnesium aldolate was converted from a predominantly syn product to a predominantly anti product in good to excellent selectivity. Representative examples are listed in Table I.

The use of CMDA had the disadvantage of occasionally causing reduction of aldehydes to alcohols[12] under reaction conditions and giving low yields of the aldol products when aliphatic aldehydes were used. However, with aromatic aldehydes the CMDA procedure gave both good yields and selectivities (entries 8, 13, and 14).

The problems associated with CMDA were overcome by utilizing $MgBr_2 \cdot OEt_2$ in conjunction with LDA. In all cases the isolated yields range from 50% to 86% and the anti:syn diastereoselection from 77:23 (entry 5) to greater than 99:1 (entry 13). As expected, the equilibration time was dependent on the substitution patterns on both the ketone and the aldehyde. It is of particular interest to compare the effect of the aldehyde substituent (R) on both the rate of equilibration and the product ratio when R (in 3 and 4, Scheme I) is phenyl vs a straight-chain substituent such as *n*-pentyl group (entry 1 vs 3 and 13 vs 14) or vs a branched-chain substituent such as an isopropyl group (entry 5 vs 6). The syn product resulting from reaction of *tert*-butyl ethyl ketone and benzaldehyde (R = Ph, R′ = *t*-Bu) (entry 13) was converted exclusively to the anti product in a good yield after adding $MgBr_2 \cdot OEt_2$ and allowing the mixture to stir for 6 h at room temperature. On the other hand, for the reaction of the same ketone and hexanal (R = *n*-pentyl, R′ = *t*-Bu) (entry 14), the rate of equilibration was very slow (48 h) and the equilibrium ratio was only about 4:1 in favor of the anti product with a lower isolated yield of 50%. The same trend was observed from reaction of propiophenone with benzaldehyde (entry 1) vs hexanal (entry 3) and from isopropyl ethyl ketone with benzaldehyde (entry 10) vs hexanal (entry 12). For 3-pentanone, the anti selectivity was better with isobutyraldehyde (entry 6) than with benzaldehyde (entry 5). Therefore, increasing the steric demand of R in the above examples resulted in faster and more efficient equilibration. However, increasing the steric bulk of the ketone substituent (R′) from isopropyl to *tert*-butyl decelerated the equilibration rate by a similar factor whether the aldehyde was aliphatic or aromatic but did not affect the equilibrium ratio: compare entries 10 vs 13 and 12 vs 14. The equilibration was also carried out with substrates other than ethyl ketones (entries 8, 9, and 15).

The order of the addition of magnesium bromide is not crucial. No real differences were observed when $MgBr_2 \cdot OEt_2$ was added to the lithium enolate of isopropyl ethyl ketone (presumably to form the bromomagnesium enolate) prior to addition of aldehyde (entry 11) vs adding it after formation of the lithium aldolate (entry 10).

The reaction gave the best results when at least 1 molar equiv of magnesium bromide etherate relative to the aldolate was used. Routinely, 1.25 molar equiv were em-

(9) Systematic studies dealing with the stereoselectivity of aldol equilibrium processes have not been reported. (a) Dubois and Fellmann have reported a single example of an aldol equilibrium. The case in question involves the reaction of 4-(bromomagnesio-2,2-dimethylpentanone with benzaldehyde to produce the anti (threo) product in a greater than 95:5 ratio: Dubois, J. E.; Fellmann, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1972**, *274*, 1307. (b) House et al. report the equilibration of phenylacetone (zinc) enolates with butyraldehyde, giving an apparently good syn:anti product ratio (~9:1). However, since the addition reaction was accompanied by at least 20% dehydration, no reliable conclusions can be drawn regarding the stereoselectivity of this reaction: House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310. (c) In Ref 3a, Heathcock et al. compared the equilibration behavior of three systems using either 1.0 equiv of lithium or 0.5 equiv of zinc aldolates. They also introduced the use of chloral as an adjunct for achieving erythro:threo equilibrations. (d) In ref 3a, addition of 0.5 equiv of $ZnCl_2$ to the propiophenone/benzaldehyde system produces an equilibrium ratio of 75:25 in an undisclosed yield.

(10) The fact that these processes are equilibrations was readily established by removing aliquots and monitoring isomer ratios over time.

(11) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345.

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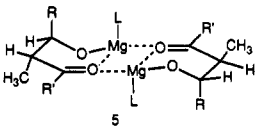
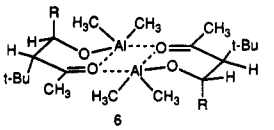
ployed. Using half a molar equiv resulted in both lower diastereomeric ratio and lower yield (entry 1 vs 2). These results differ from those using Zn(II) in equilibration reactions where 0.5 molar equiv of Zn(II) gave better diastereoselectivity.[9b] In one comparative experiment, the use of $ZnBr_2$ in the aldol reaction between propiophenone and benzaldehyde gave a lower anti:syn ratio (92:8) and lower yield (53%) than the reaction with $MgBr_2 \cdot OEt_2$ (98:2, 73%).[3a,9d]

The equilibration of lithium aldolate is often accompanied by lower yields of aldol products as a result of retro-aldol reaction.[3a,9b] This complication is effectively eliminated with the use of Mg(II). We postulate that the strongly chelating magnesium ion permits isomerization around the C_2–C_3 bond without requiring the complete dissociation of the adduct from the metal. However, this still leaves a pivotal question unanswered, i.e., why are the observed anti selectivities as high as they are? As House pointed out almost twenty years ago,[9b] anti adducts are thermodynamically more stable than their syn counterparts, *but only to the extent of having one less skew butane interaction.* We suggest that bis-adducts, such as **5**, may provide a mechanism for amplifying what might otherwise be small energy differences between monomeric aldolate diastereomers. For example, a hypothetical equilibrium mixture of 5:1 anti–anti:anti–syn bis-aldolates would result in an 11:1 anti–syn product ratio. Support for the intermediacy of dimeric aldolate comes from the work of Jeffery et al., who have isolated and characterized aluminum aldolate dimers of general structure **6**.[13]



5



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Experimental and theoretical studies aimed at establishing the intermediacy of bis-magnesium adducts in these reactions is underway. In addition, we are also exploring the potential of this procedure with regard to simple aldol selectivity and double asymmetric induction.

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(13) See: Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem.* **1974**, *74*, 373 and references contained therein.

Stereoselective Synthesis of Trisubstituted α,β-Unsaturated Esters and Amides via Reactions of Tantalum–Alkyne Complexes Derived from Acetylenic Esters and Amides with Carbonyl Compounds

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Summary: Treatment of acetylenic esters with low-valent tantalum ($TaCl_5$ and Zn) in DME and benzene produces tantalum–alkyne complexes (not isolated), which react with carbonyl compounds regioselectively at the α-position of the esters to give *Z* isomers of trisubstituted α,β-unsaturated esters in a stereoselective manner. In contrast, tantalum–alkyne complexes derived from acetylenic amides react with carbonyl compounds at the β-position of the amides predominantly.

Tri- or tetrasubstituted α,β-unsaturated carbonyl compounds, in particular, esters and amides, are an important class of compounds as synthetic intermediates of many natural products. Stereoselective construction of such compounds is a fundamental challenge in organic synthesis.[1,2] Olefination of carbonyl compounds using Horner–Emmons reagents or the carbanions stabilized by silicon and ester groups usually produces a mixture of *E* and *Z* isomers of α,β-unsaturated esters.[3] Carbometalation of a propiolate ester with lithium dialkylcuprates followed by addition of carbonyl compounds affords (*Z*)-2-alkylidene-3-hydroxy esters stereoselectively in the case of ketones, while its condensation reaction with aldehydes affords mixture of *E* and *Z* isomers.[4]

Recently we found a convenient procedure for the preparation of tantalum–alkyne complexes[5,6] and employed the complexes as a cis-fixed vicinal alkene dianion reagent.[7] We disclose here novel access to trisubstituted α,β-unsaturated esters and amides by the reaction of tantalum–alkyne complexes, derived from acetylenic esters or amides, with carbonyl compounds.

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