Journal of Advances in Science and Technology

Vol. IV, No. VIII, February-2013, ISSN 2230-9659

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Journal of Advances in Science and Technology
Vol. IV, No. VIII, February-2013, ISSN 2230-9659

Mechanisms of the Nickel- And Cobalt-Catalyzed Reductive Aldol Cyclization’s

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Abstract – In the presence of diethylzinc as a stoichiometric reductant, substoichiometric quantities of an appropriate cobalt source catalyse diastereoselective reductive aldol coupling reactions of a,b-unsaturated amides with ketones. The use of a readily available oxazolidine as a chiral auxiliary imparts high levels of asymmetric induction in these reactions.

The cobalt-catalysed alkylative aldol cyclisations of unsaturated amides with an appendant ketone were studied using a range of trialkylaluminium reagents. Investigations revealed that Co(acac)2·2H2O acts as an effective precatalyst for this transformation and the reaction provides hydroxylactam products containing three contiguous stereocentres with high levels of diastereoselection. The substrate scope of the reaction was explored and attempts were made to develop an asymmetric variant of this process. Two plausible reaction mechanisms have been proposed; the first invokes a allylcobalt species as a key intermediate in the reaction mechanism and the second involves a radical-mediated pathway.

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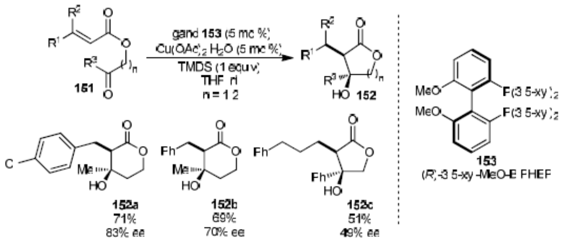
INTRODUCTION

The reductive aldol reaction, in which an aldehyde or ketone undergoes reaction with an enolate generated in situ by the conjugate reduction of an a,b-unsaturated carbonyl compound, is a powerful and well-established method of carbon–carbon bond formation.1,2 Using various metal precatalysts and stoichiometric reductants that include silanes, triethylborane and molecular hydrogen, a wide variety of inter- and intramolecular reductive aldol reactions have been described.1,2 A recent major development in this area is the ability to control the absolute stereochemistry of the products through the use of substoichiometric quantities of chiral metal–ligand complexes.

One contribution to this field from our research group has been the development of both inter- and intramolecular reductive aldol reactions that employ diethylzinc as the stoichiometric reductant, in conjunction with cobalt3 or nickel4 precatalysts. An advantageous feature of these conditions is the ability to promote high-yielding reactions between b-substituted a,b-unsaturated carboxylic acid derivatives and ketones, reaction partners that are situated on the lower end of the reactivity scale in reductive aldol reactions. In this paper, we provide a full account of the intermolecular reactions3b promoted by Et2Zn in combination with a cobalt source, along with extension to an asymmetric variant using a chiral oxazolidine auxiliary.

Reductive aldol cyclisations have been a key research interest of the Lam Group for a number of years. Our earliest examples comprised of copper-catalysed systems that employed siloxanes as the stoichiometric reductant. The use of chiral phosphine ligands allowed the preparation of enantioenriched _-hydroxylactones.

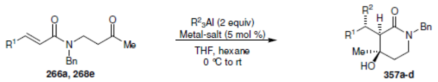


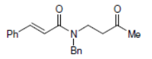
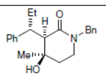
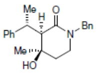
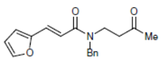
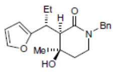
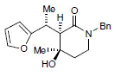
Further investigations revealed that the copper-catalysed methodology was effective for substrates containing an amide tether. However, the scope of the reaction was limited to those possessing a hydrogen or a methyl group at the β-position of the α,β-unsaturated amide.

The copper-catalysed methodology was used to prepare a series of 4-hydroxypiperidin-2-ones in a highly diastereoselective fashion. The presence of a pre-existing stereocentre in the substrate did not adversely affect the diastereoselectivity of the reductive aldol reaction. A reductive removal of the carbonyl group provided access to piperidine structures, which feature in many biologically active compounds.

OBSERVATIONS

We decided to employ other stoichiometric reductants to see how they would alter the reaction. When trialkylaluminiums were used as reagent, interestingly, only alkylative cyclisations were observed in both of the metal salts utilised on substrates 266a and 268e. The diastereoselectivities were very high (>19:1) and the reactions were very clean. When Et3Al was used (entries 1-2 and 5-6) the products where isolated in good yields. When Me3Al was used (entries 3-4 and 7-8) the reaction proceeded cleanly giving ca. 100% conversion: however when the crude mixtures were purified by column chromatography, isolated yields were low. We could not find a solution to this problem. It is worth mentioning that the use of Me2Zn did not lead to a cyclisation and the starting materials were recovered.



Entry	Metal	Substrate	R²		Yield(%)^b
1	Co(acac)$_2$·H$_2$O	 266a	Et	 357a	99
2	Ni(acac)$_2$		Et		97
3	Co(acac)$_2$·H$_2$O		Me	 357b	62
4	Ni(acac)$_2$		Me		57
5	Co(acac)$_2$·H$_2$0	 268e	Et	 357c	96
6	Ni(acac)$_2$		Et		90
7	Co(acac)$_2$·H$_2$O		Me	 357d	51
8	Ni(acac)$_2$		Me		45

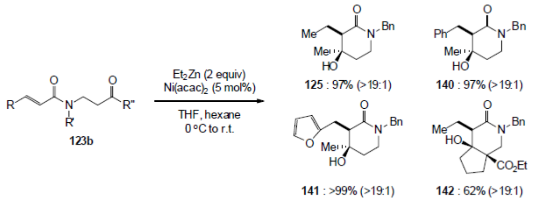
a) all reaction performed in 0.2 mmol scale b) isolated yield

Table. Alkylative Cyclisations

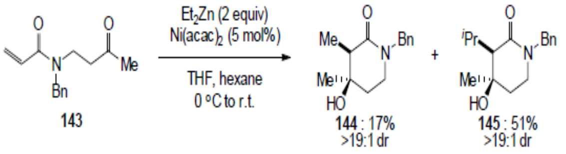
The relative stereochemistry of compound 357a was determined by X-ray crystallography. The stereochemical outcome can be explained by observing the Zimmerman–Traxler-type transition states 358a and 358b. A minimised syn-pentane interaction seems to be the dominating factor in determing the stereochemistry. A transition state leading to product 359 would have minimised A1,3-strain, but this product was not observed.

NICKEL-CATALYSED REDUCTIVE ALDOL REACTIONS

Alongside the cobalt catalysis described above, Lam developed a complementary nickel catalysed intramolecular reductive aldol reaction forming β-hydroxylactams and β-hydroxylactones, again using a diethylzinc as a stoichiometric reductant. This nickel-catalysed reductive aldol reaction showed higher reactivity than the cobalt system; substrates which had previously shown little or no reactivity now gave the desired products.



A problem encountered with this nickel system is that of competitive alkylative aldol reaction, a side reaction which is not observed under cobalt catalysis. Substrate 143 gave reductive aldol product 144 in 17% yield and alkylative aldol product 145 in 51% yield. Lam found that this competitive alkylation is eliminated by the addition of α- or β-substituents on the acrylamide.



The synthesis of six-membered β-hydroxylactones was also successful under nickel catalysis, a transformation which was found not to be possible under the comparable cobalt reductive conditions; the results observed were comparable to those shown with the keto-acrylamides. However, a significant quantity of the alkylative aldol product was observed with electron-deficient substrates.

NICKEL-CATALYSED REDUCTIVE DIECKMANN CONDENSATION

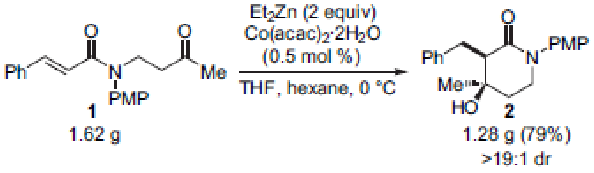
A solution of Ni(acac)$_2$ (2.7 mg, 0.01 mmol, 5 mmol%) and *tert*-butyl 2-((benzyl(2-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)-2-oxoethyl)amino)methyl)acrylate 292 (88.7 mg, 0.2 mmol) in tetrahydrofuran (3 mL) was stirred at room temperature for 15 minutes before cooling to 0 ^{o}C. Diethylzinc (1 M in hexanes) (400 μL, 0.4 mmol) was added to the solution, the reaction mixture was stirred at ambient temperature for 16 hours. 1 M HCl$_{(aq)}$ (1 mL) was added to the reaction mixture and the resulting solution was stirred for 15 minutes. The reaction mixture was dissolved in diethyl ether (25 mL) and washed with saturated sodium hydrogen carbonate (2 x 25 mL), water (25 mL) and saturated brine (25 mL). The organic phase was extracted, dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by flashed column chromatography (12:1 petrol:diethyl ether) to give *tert*-butyl 1-benzyl-4-oxo-3-propylpyrrolidine-3-carboxylate 310 as a colourless oil (18.3 mg, 29% yield) followed by 258 as a colourless oil (38.7 mg, 67%).

Data for 258: HPLC Diacel Chiralpak OJ, hexane/propan-2-ol (99:1), 0.5 mL/min (220 nm, 30 ^{o}C): t_R (minor) = 14.6 min, t_R (major) = 15.6 min, 18%

ee. All other spectroscopic data identical to that previously reported.

RESULTS AND DISCUSSION

During ongoing efforts to develop new catalyst systems for the diastereoselective synthesis of β-hydroxylactones and lactams using reductive aldol cyclisations, we recently established the exceptional ability of Co(acac)$_2$.$_{2H2O}$/Et2Zn in promoting reactions of substrates that were problematic under previously reported conditions using copper catalysis



Whether the Co(acac)$_2$.2H$_2$O/Et$_2$Zn combination could also be applied to the corresponding intermolecular reductive aldol reactions was an important issue to address, and with this consideration in mind, the reaction of N,N-dimethylacrylamide with acetophenone was conducted. This experiment was successful, andprovided the aldol product 4a^7 in 75% yield, accompanied by the diastereomeric product (not shown), in a 5:1 ratio. The use of 4-acryloylmorpholine as the pronucleophilic component provided very similar results.

Further examination of substrate scope revealed that acetophenone derivatives containing alkyl, methoxy or bromo substituents were competent electrophiles in these reactions, providing tertiary alcohol-containing aldol products with up to 9:1 diastereomeric ratio and 85% isolated yield of the major diastereomer. ortho-Substitution in the acetophenone was found to result in enhanced levels of diastereoselection. However, the reaction of 4-nitroacetophenone with provided none of the desired product 4g, with a complex mixture being obtained instead. Presumably, the highly electron-deficient nature of this particular ketone leads to deleterious side reactions under these conditions.

CONCLUSION

Possible mechanisms for transition metal-catalysed-reductive cyclisations have been discussed, and a deuterium labeling study designed to probe the stereochemical outcome of cyclisation within the context of these mechanisms has revealed the complex nature of these reactions. Even that the experiments performed provided plenty of information of the possible mechanism of the reaction, further work is needed to further clarify it. An interesting class of fully alkylative cyclisations were also discovered by a change of the reductant Et$_2$Zn to R$_3$Al.

Cobalt-catalysed conjugate reduction of α,β-unsaturated amides using diethylzinc as the stoichiometric reductant generates zinc enolates that participate in efficient aldol couplings with ketones, providing tertiary β-hydroxycarbonyl products. A wide range of substitution at the β-carbon of the α,β-unsaturated amide is tolerated, and best results in terms of diastereoselectivity are obtained with aromatic ketones such as acetophenone derivatives. Although aliphatic ketones were found to undergo the reductive aldol reaction, their reactions exhibit no diastereoselectivity.

Although a readily accessible N-phenylglycinol-derived chiral auxiliary was found to impart high levels of asymmetric induction in these reactions, all attempts to cleave the oxazolidine from the products have been unsuccessful due to the sterically hindered nature of the products, coupled with the presence of relatively sensitive tertiary benzylic alcohols. However, this study has defined structural features for an auxiliary that gives high levels of asymmetric induction, and provides useful information that might aid in the design of improved auxiliaries in future.

A novel cobalt-catalysed alkylative aldol cyclisation of α,β-unsaturated amides with a pendant ketone has been described, using a range of different trialkylaluminium reagents. It is significant that, prior to our work, there were no literature reports of metal-catalysed conjugate addition of trialkylaluminium reagents to α,β-unsaturated amides. The reaction generally proceeds with high levels of diastereoselection and provides β-hydroxylactam products in good yields. Attempts to further expand the substrate scope have been discussed and the use of chiral non-racemic ligands has not imparted any enantioselectivity to the reaction, although the reasons for this have not yet been elucidated. Various mechanistic pathways have been postulated including one involving a π-allylcobalt species and the other comprising of a radicalmediated pathway. A stereochemical rationale has been proposed to account for the high diastereoselectivity of the reaction, which suggests syn-pentane strain is the dominant stereocontrol element.

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