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Me_2Zn-Mediated Catalytic Enantio- and Diastereoselective Addition of TosMIC to Ketones

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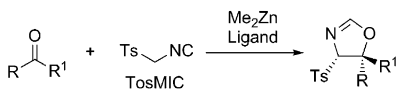
Abstract: The first catalytic asymmetric addition of TosMIC to unactivated ketones is presented. A combination of Me_2Zn and aminoalcohol catalyst promoted the aldol addition/cyclization reaction to render oxazolines possessing a fully substituted stereocenter with excellent yields (up to 92%), high enantioselectivities (up to 96%), and complete diastereoselectivity. The chiral oxazolines were then used to give, after a straightforward acid hydrolysis, enantioenriched building blocks bearing tertiary alcohol motifs such as hydroxylaldehydes, hydroxylacids, and hydroxylesters without racemization.

The amphoteric nature of isocyanides allows their use in the synthesis of numerous important classes of nitrogen-containing heterocyclic compounds.[1] Recently, isocyanide-involved multicomponent and cascade reactions have also been developed.[2] Since the pioneering work of Ito and Hayashi,[3] the addition of isocyanides, isocyanoacetate,[4] and TosMIC (*p*-toluenesulfonylmethyl isocyanide)[5] have shown exceptional reaction diversity and broad synthetic potentiality.[6] Many organometallic[7] or organocatalyzed[8] asymmetric additions of isocyanides to different electrophiles have been described. In principle, prochiral ketones serve as versatile substrates for the generation of fully substituted stereocenters. As is anticipated by their reduced reactivity and stereochemical selectivity towards nucleophilic addition, ketones remain daunting substrates in stereoselective addition reactions.[9] Interesting methodologies for the addition of enolates to unactivated ketones have been reported in the literature.[10] In this perspective, Dixon described the first highly enantio- and diastereoselective aldol addition/cyclization reaction of isocyanoacetate esters with unactivated prochiral ketones to afford functionalized oxazolines with a fully substituted stereocenter.[11] Shibasaki reported a powerful yet atom-economical direct catalytic enantioselective aldol addition of α-substituted α-isothiocyanates to simple ketones.[12] Moreover, 3-Isothiocyanato oxindoles were also found to be suitable reagents for a direct addition to ketones, promoted by bifunctional thiourea–tertiary amine catalysts.[13] However, despite all the efforts dedicated to the synthesis of enantioenriched tertiary alcohols by the addition of nucleophiles to ketones,[14] enantioselective addition of TosMIC to ketones is still a formidable challenge.[15] We describe herein the first Me_2Zn and chiral aminoalcohol-based catalytic system for highly enantio- and diastereoselective addition of TosMIC to unactivated ketones. This asymmetric aldol addition/cyclization protocol gives rise to functionalized oxazolines possessing a fully substituted stereocenter (Scheme 1). Oxazolines are simple heterocyclic compounds with diverse synthetic varsity and, in addition, upon a mild hydrolysis they become prominent substrates for the synthesis of many highly substituted and enantioenriched products.



Scheme 1. Addition of TosMIC to ketones promoted by chiral zinc complexes.

In the past our group has reported Reformatsky reactions[16] and the catalytic enantioselective aldol-type addition of ethyl diazoacetate to ketones[17] promoted by Me_2Zn and chiral ligands. Me_2Zn proved to be a suitable reagent for the deprotonation and activation of nucleophiles in the presence of aminoalcohols. We reasoned that these conditions were also suitable for isocyanoacetate and TosMIC. Therefore, to prove this supposition, we investigated the nucleophilic addition of isocyanides and chose acetophenone as the model substrate. Pleasingly, the reaction with TosMIC in a catalytic system that comprised procatalyst (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol (20 mol%) and Me_2Zn (1.7 equiv) was highly diastereoselective and only the *trans*-configured oxazoline was isolated. Unfortunately, reaction with isocyanoacetate under the same reaction conditions gave a mixture of diastereoisomers.[18]

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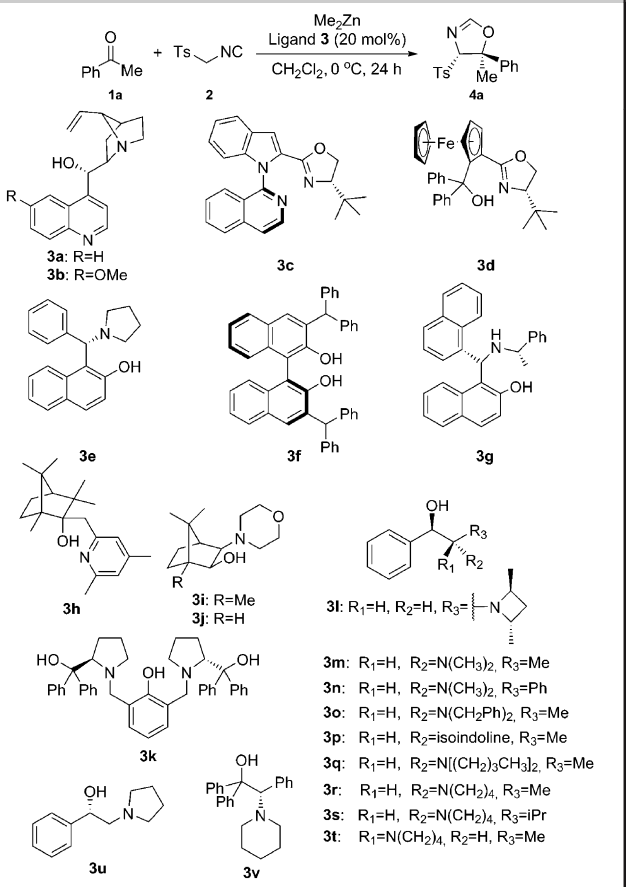
Inspired by this excellent diastereoselective reaction, along with an aim of achieving enantioenriched oxazolines, we tested several commercially available or easy to synthesize chiral ligands in the model reaction involving TosMIC and acetophenone at 0 °C. Although the oxazolines were formed with complete simple diastereoselection, conversion, and facial stereoselection of the reactions were discouraging (Table 1, entries 1–13). Gratifyingly, enantioselectivity was increased significantly, up to 69% *ee*, when the ligand **3m** was employed. Therefore, we examined other 1,2-aminoalcohols containing a benzylic alcohol motif, under the selected reaction conditions. Replacing the methyl by a phenyl at the R^3-position of ligand **3m** leads to a remarkable decrease in the *ee* and conversion (entry 14). Subsequently, by keeping methyl at the R^3-position constant and changing R^2 substituents to more bulkier groups, such as *N,N'*-dibenzylamine, we observed the decrease of *ee* up to 22% (entry 15). Further optimization using aliphatic substituents at the R^2-position resulted in a very good *ee* (72% *ee*, entries 16–18). Even though **3q** and **3r** show the same activity and selectivity, we chose **3r** for further studies because of the ease of availability of its structural variants. Enantioselectivity of this reaction was influenced not only by the nature of substituents at the R^1-position but also by the relative configuration of the two stereocenters; (1*R*,2*S*)-chiral aminoalcohol gave 72% *ee*, whilst the (1*R*,2*R*)-proligand resulted in only 48% *ee* (entries 18 and 20). Replacing the methyl in the ligand **3r** with an *i*Pr resulted in a poorer *ee* (entry 19, 12% *ee*).

It is worth noting that the ligand **3u** (in which R^1, $R^2 = H$) and **3v** which possesses the group $\{(CPh_2)_2\}$ did not increase the selectivity.[19] From this observation, the commercially available (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol (**3r**) was found to be an optimum ligand for the asymmetric addition of TosMIC to acetophenone.

The effect of solvent on the catalytic asymmetric addition of TosMIC to acetophenone reveals that DCM was a suitable solvent for higher enantioselectivity and reactivity (Table 2, entries 1–3). Reaction temperature was found to be optimum at 0 °C, as so significant quantities of products were isolated at −20 °C whilst unwanted side reactions were observed at room temperature.

The limiting agent for the reaction was the TosMIC. The amount of acetophenone was also found to be crucial; when it was reduced in to one equivalent, the outcome of the reaction resulted in a low *ee* and conversion (Table 2 entry 6, 30% conv., 39% *ee*). In comparison, the more reactive Et_2Zn increased the enantioselectivity (78%), but unfortunately it also accelerated the side reaction which generated unidentified impurities. A better conversion was obtained by increasing the equivalents of Me_2Zn and decreasing the concentration of TosMIC by slow addition of a dilute solution of TosMIC in DCM by a dropping funnel. The addition of TosMIC by syringe pump gave rise to the formation of the impurities with a decrease in *ee* and yield, probably caused by the presence of a trace of air. Finally, a study of the catalytic loading showed that 25 mol% was the optimum. It gave the highest enantiomeric excess (85% *ee*) on the model reaction. The enantiomeric excess decreased slightly both by increasing (83% *ee* with 30 mol%) and lowering the amount of the ligand to 10 mol% (76% *ee*).

Table 1. Catalyst screening for the asymmetric aldol addition/cyclization reaction of acetophenone **1a** and toluenesulfonylmethyl isocyanide (TosMIC) (**2**).[a]

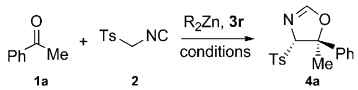


Entry	3	Conv. [%][b]	*ee* [%][c]	Entry	3	Conv. [%][b]	*ee* [%][c]
1	**3a**	10	5	12	**3l**	–	10
2	**3b**	12	20	13	**3m**	45	69
3	**3c**	–	14	14	**3n**	10	10
4	**3d**	10	33	15	**3o**	–	22
5	**3e**	–	0	16	**3p**	18	70
6	**3f**	–	6	17	**3q**	45	72
7	**3g**	8	0	18	**3r**	45	72
8	**3h**	15	15	19	**3s**	40	12
9	**3i**	–	0	20	**3t**	50	48
10	**3j**	–	0	21	**3u**	50	62
11	**3k**	9	27	22	**3v**	8	52

[a] All the reactions were performed in the presence of 20 mol% **3**, 1.7 equiv of Me_2Zn, 0.1 mmol of TosMIC, and 0.2 mmol of acetophenone in dichloromethane at 0 °C for 24 h. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase.

The scope of the asymmetric aldol reaction of TosMIC catalyzed by the chiral aminoalcohol/Me_2Zn system was evaluated. Thus a number of unactivated ketones were selected and subjected to the optimized reaction conditions (Table 3). The reaction was compatible with significant structural variations of ketones. Notably aromatic, aliphatic, heterocyclic, and ferrocenyl ketones were all well tolerated and resulted in only the *trans*-

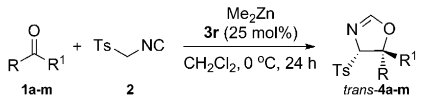
Table 2. Me_2Zn-mediated addition of TosMIC to acetophenone promoted by chiral zinc complexes.



Entry	Sol.	**3r** [mol%]	R_2Zn (equiv)	Conv. [%][a]	*ee* [%][b]
1	DCM	20	Me_2Zn (1.7)	45	72
2	THF	20	Me_2Zn (1.7)	5	50
3	toluene	20	Me_2Zn (1.7)	35	50
4[c]	DCM	20	Me_2Zn (1.7)	12	40
5[d]	DCM	20	Me_2Zn (1.7)	5	40
6[e]	DCM	20	Me_2Zn (1.7)	30	39
7	DCM	20	Et_2Zn (1.7)	57	78
8[f]	DCM	20	Me_2Zn (1.7)	–	76
9[g]	DCM	20	Me_2Zn (6)	50	80
10[g]	DCM	20	Me_2Zn (8)	81	83
11[g]	DCM	20	Me_2Zn (10)	100	82
12[h]	DCM	20	Me_2Zn (10)	50	82
13[g]	DCM	10	Me_2Zn (10)	100	76
14[g]	DCM	25	Me_2Zn (10)	100	85
15[g]	DCM	30	Me_2Zn (10)	100	83

[a] Determined by ^1H NMR analysis of the crude reaction mixture. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Reaction at room temperature [d] Reaction at −20 °C. [e] Reaction with 1 equiv acetophenone. [f] Slow addition of TosMIC by using a syringe pump. [g] Addition of TosMIC in 2 mL of DCM from dropping funnel 0.5 mL h^{-1}. [h] Addition of TosMIC in 2 mL of DCM from a dropping funnel 1 mL h^{-1}.

Table 3. Scope of asymmetric aldol reaction with different ketones.[a]



Entry	Ketone **1**	**4**	Yield [%][b]	*ee* [%][c]
1	acetophenone	**4a**	57	85
2	2-methylacetophenone	**4b**	90	74
3	2-bromoacetophenone	**4c**	80	88
4	4-methoxyacetophenone	**4d**	80	86
5	2-acetonaphthone	**4e**	85	84
6	2-bromo-2′-methoxyacetophenone	**4f**	92	50
7	1-tetralone	**4g**	80	90
8	4-methoxy-1-tetralone	**4h**	65	90
9	1-indanone	**4i**	75	82
10	1-acetylferrocene	**4j**	90	96
11	1-ferrocenylethylketone	**4k**	60	86
12	2-acetylbenzofuran	**4l**	85	77
13	cyclohexanone	**4m**	92	62
14	pinacolone	**4n**	91	12

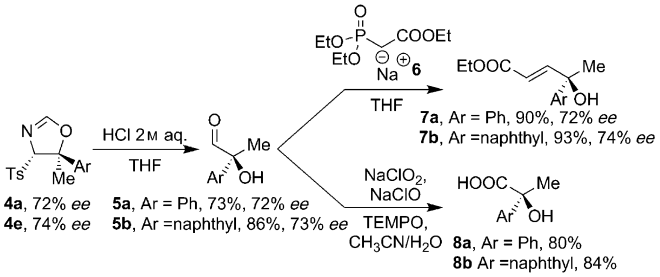
[a] All the reactions were performed with 0.1 mmol of TosMIC **2**, 0.2 mmol of ketone **1**, 25 mol% of **3r**, and 10 equiv of Me_2Zn in dichloromethane at 0 °C for 24 h. [b] Isolated yield after chromatography. [c] Determined by HPLC on a chiral stationary phase.

oxazolines with good to excellent yields and enantioselectivities (up to 92% yield and 96% *ee*) at 0 °C in 24 h. The acetophenone and its derivatives gave very good yields and enantioselectivities (Table 3, entries 2–4, 74–88% *ee*). With six-membered cyclic ketones such as α-tetralone and its derivatives, very good enantioselectivities (90% *ee*) were observed. A remarkable success was achieved when acetylferrocene was tested. The corresponding *trans*-oxazoline was formed with excellent enantiomeric excess and a high yield (Table 2, entry 10, 96% *ee*, 90% yield).

A possible mechanism for the reaction is reported in the Supporting Information. In our mechanistic picture, Me_2Zn is the deprotonating reagent that is able to form the corresponding MeZn–TosMIC intermediate. The ability of the chiral zinc-alkoxide to coordinate both ketone and MeZn–TosMIC produces the stereoselective reaction. In the final stage of the catalytic cycle, a MeZn–oxazoline is postulated. This hypothesis was investigated by deuteration experiments. A selective introduction of a deuterium atom on the imino carbon atom of oxazoline was achieved when the intermediate was quenched with D_2O, supporting our rationale (see the Supporting Information for full details). The relative configuration of the product *trans*-oxazoline **4a** was assigned through Nuclear Overhauser effect spectroscopy (NOESY) and assumed by analogy for all other products obtained. The absolute configuration is determined as 4*S**,5*S** by simulation of the Electronic Circular Dichroism (ECD) spectrum of compound **4c** by means of TD-DFT simulation and further confirmed by the comparison of the hydrolyzed product **5a** with reported compounds.[20]

Traditionally, TosMIC was used as a precursor in the synthesis of heterocycles, but other interesting compounds such as α-hydroxyaldehydes can also be obtained.[21] Van Leusen reported[22] a PTC-based stereospecific method involving a diastereoselective reaction with enantiopure chiral TosMIC derivatives for the synthesis of 2-hydroxy-2-phenylpropanal. Upon an acid hydrolysis of enantioenriched 2-oxazolines, this method provided the desired products in 31% *ee*. The synthetic utility of our method allows the preparation of fully substituted enantioenriched α-hydroxyl aldehydes as versatile starting materials. To illustrate the possibility offered by this methodology, we hydrolyzed the oxazolines **4a** and **4e** by using a mixture of aqueous 2 M HCl and THF. The resulting α-hydroxyaldehydes **5a** and **5b** were isolated with no racemization observed[23] (Scheme 2). The absolute configuration for the compound **5a** was assigned based on the optical rotation of the known compound.[24] This also confirmed the assignment of the absolute configuration carried out by ECD and DFT simulations. The reaction with phosphonate **6** under standard Horner–Wadsworth–Emmons conditions gave the highly functionalized derivatives **7a**,**b** with no racemization. In addition, **5a**,**b** can be oxidized to the corresponding α-hydroxylacids bearing a fully substituted stereocenter in a straightforward manner.

In conclusion, we have developed the first catalytic enantioselective addition of TosMIC to various unactivated ketones by using Me_2Zn and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol. The commercially available ligand and Me_2Zn make this method highly attractive and an easy route to access many chiral *trans*-oxazolines bearing a fully substituted stereocenter. Through a mild acid hydrolysis of the product oxazolines, this method enables the synthesis of more elaborate, valuable organic building blocks in a straightforward manner from unactivated ketones without racemization. Application of this chemistry towards the addition of other isocyanides to ketones



Scheme 2. Transformation of the products **4a**,**e** in to useful starting materials. TEMPO = 2,2,6,6-tetramethylpiperidine *N*-oxide.

and other electrophiles is under active investigation in our laboratory and will be reported in due course.

Experimental Section

General method

In a 50 mL Schlenk flask, **3r** (0.025 mmol, 5.1 mg) was dried and dissolved in DCM (2 mL). The mixture was cooled to 0 °C and then a solution of Me_2Zn (1 mmol, 2 M in toluene) was added. After stirring for 30 min at the same temperature, acetyl ferrocene (0.2 mmol, 45.6 mg) was added under a flow of nitrogen. Roughly 5 min later a solution of TosMIC (0.1 mmol, 19.5 mg) in DCM (5 mL) was added to the reaction mixture from a pressure equalizing dropping funnel (10 mL, with a Rotaflow stopcock) at a rate of 1 mL min^{-1} under anhydrous conditions. A positive pressure of nitrogen was maintained inside the flask throughout the reaction. The reaction mixture was stirred magnetically for 24 h at 0 °C and quenched with 10 mL of cold water. The organic layer was separated and the aqueous layer was extracted with DCM (3×5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4, and filtered through a pad of Celite and concentrated under reduce pressure.

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Keywords: addition reactions · enantioselectivity · ketones · Me_2Zn · TosMIC

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