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Graphical Abstract

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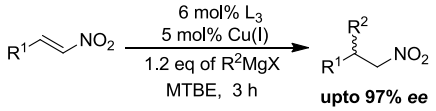

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Enantioselective Grignard addition to nitroolefin

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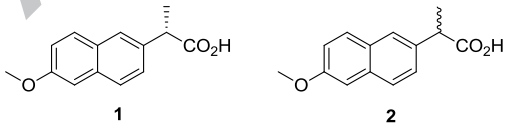
ABSTRACT

A novel synthesis of naproxen utilizing nitro aldol, 1,4-addition and Nef reaction is demonstrated where the desired *S*-enantiomer is achieved by resolution. Further to this first enantioselective 1,4-addition of Grignard reagent to nitroolefin is demonstrated to synthesize derivatives of naproxen.

Naproxen **1** as shown in Figure 1 is a nonsteroidal anti-inflammatory drug (NASAID)[1] meant for the treatment of pain, fever and inflammation. Although, there are myriad approaches[2] that have been developed for **1**, majority of them useprocess shown in Scheme 1,[3]that involves overall five tedious steps. In particular, synthesis of **1**starts with 2-acetyl-6-methoxy naphthalene **7**, which upon Darzen condensation in the presence of potassium secondary butoxide with isopropylester of chloroacetic acid followed by hydrolysis and decarboxylation afforded 2-(6-methoxynaphthalen-2-yl)propanal **5**. Thereafter, the condensation of **5** with hydroxyl amine in presence of sulfuric acid followed by dehydration and hydrolysis with caustic lye afforded the *racemic* naproxen **2** via **4** and **3**.



1 2

Figure1. Naproxen framework

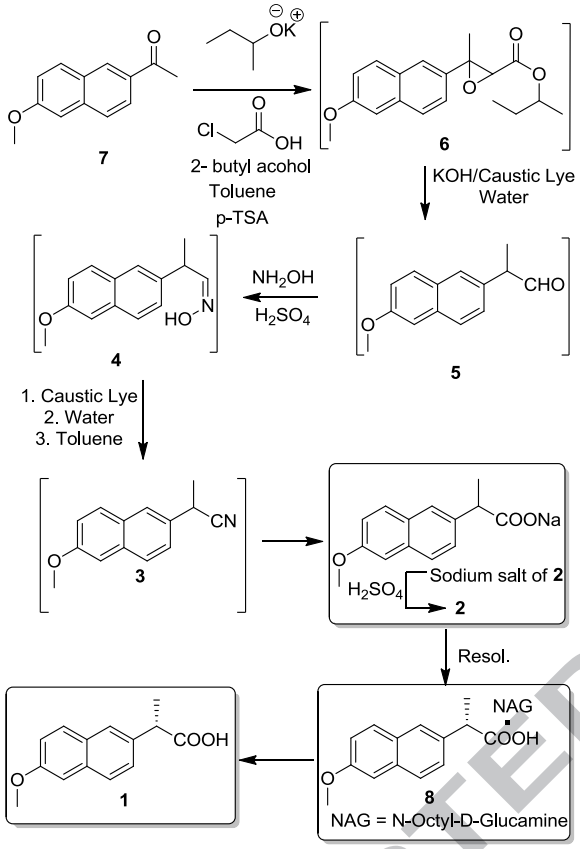
In our endeavor, we attempted to develop an enantioselective synthesis of **1**. In this effort, we end up unearthing first enantioselective Grignard addition to nitroolefin. Interestingly, enantioselective 1,4-addition of organometallic reagents to nitroolefin or enones is indeed one of the most elegant methods for the synthesis of enantiomerically pure substituted nitroalkanes or saturated ketones/aldehydes. Nevertheless, there has been excellent research work published in this context.[4-6]

In order to use reactive Grignard reagents in these reactions, essentially a stoichiometric amount of a chiral additive is required to obtain a significant level of enantioselectivity.[7] Catalytic method for the asymmetric 1,2-addition of Grignard reagents has recently been reported.[8] However to the best of our knowledge a catalytic enantioselective Grignard reagent addition to nitroolefin in 1,4-fashion remains unprecedented.

Herein, we disclose novel and short formal synthesis for naproxen **1**featuring nitroaldol, dehydration, 1,4-addition and Nef reaction. Further to this first enantioselective 1,4-addition of Grignard reagents to α,β-unsaturated nitro derivatives, catalyzed by a Cu(I) and chiral ligand derived species.

The synthesis commences with the reaction of 6-methoxy-2-napthaldehyde **11** with nitromethane in

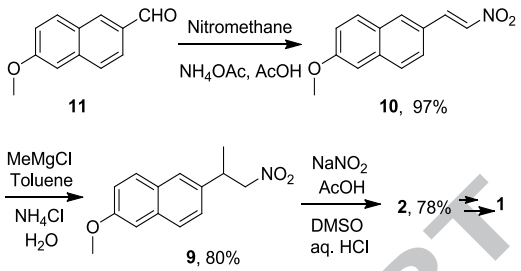
presence of base in acetic acid (*in situ* salt) at 90-100 °C for 10-12h followed by distillation of solvents under reduced pressure at <80 °C and isolation from water at pH 7. Screening of the bases (*insitu* salts) suggests that the ammonium acetate[9]is the choice of reagent for nitroaldol followed by dehydration to afford intermediate **10**.



Scheme 1. Precedented synthesis for **1**

The above isolated nitroolefin **10** was treated with 3M methyl magnesium chloride in THF at 0-5 °C in toluene for about 30-60 min. followed by quenching with ammonium chloride solution at 0-5 °C to obtain 1,4-addition product nitroalkane intermediate **9**.

Thereafter, nitroalkane intermediate **9** was subjected to Nef reaction conditions by employing sodium nitrite in acetic acid and DMSO for 24 h at 40-50 °C. After the completion of the reaction (TLC), the reaction mass was quenched into 10% hydrochloric acid, stirred for about 15 min and theproduct was extracted into toluene. The mixture of the organic layer and water, stirred about 15 min. at 25 to 35°C, adjusted pH to 13-14 with caustic lye, separated the toluene and washed with toluene to remove the impurities followed by extraction into toluene at pH 3-4. Distillation of toluene afforded *racemic* naproxen **2**.



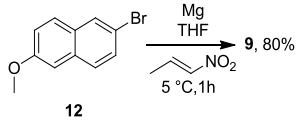
Scheme 2.Novel synthetic approach for **1**

Screening of $NaNO_2$ equivalence at 90-100 °C suggests that the 3 equiv $NaNO_2$ (Table 1; entry 2) is the optimal condition for affording the *racemic* naproxen **2**.

Table1. Nef reaction conditions

S. No.	$NaNO_2$ equiv.	Temp °C	Time(h)	%Yield of 2
1	3	70	24	72
2	**3**	**100**	**24**	**78**
3	3	120	24	78
4	4	100	24	76
5	6	100	24	75

After completing the above sequence, we were intrigued by the potential of a transformation switch strategy involving the Grignard reagent of 2-methoxy-6-bromo naphthalene **12** and its 1,4-addition onto the 1-nitroprop-1-ene to afford the intermediate **9** as shown in Scheme 3.



Scheme 3. Alternate approach to intermediate **9**

In this approach, the1-nitroprop-1-ene (*precaution: unsafe to handle; dry distillation should be avoided*) was added to the Grignard reagent of 2-methoxy-6-bromo naphthalene **12**in THFat 0- 5 °C for about 30-60 min that afforded 1,4-addition product, **9**in excellent yield.

Having gained intellectual control over reaction sequence, we decided to develop enantioselective version of 1,4-addition. In our endeavor, we screened various catalysts by involving ligands (**L_1-L_3**) and Cu(I) combinations to achieve enantioselectivity.

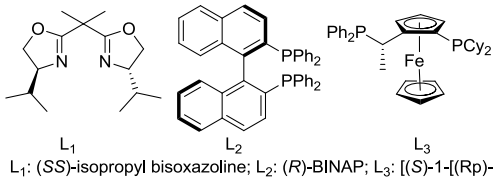
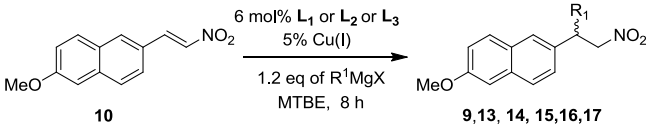


Figure 2. Structure of ligands

Table 2.1,4-Addition by using ligand $\mathbf{L_1}$, $\mathbf{L_2}$and$\mathbf{L_3}$



10 **9**,**13**, **14**, **15**,**16**,**17**

S.No.	Catalyst	R^1/X	Temp.˚C	Solvent	*er (R/S)* (HPLC)	Yield (%)	Product
1	CuTC/L_1	Me/Cl	-60	THF	50/50	75	**9**
2	CuTC/L_1	Me/Cl	-20	THF	49/51	75	**9**
3	CuI/L_1	Me/Cl	-60	THF	45/55	70	**9**
4	CuI/L_1	Me/Cl	-20	THF	49/51	70	**9**
5	$Zn(OTf)_2$/L_1	Me/Cl	-60	THF	50/50	70	**9**
6	$Zn(OTf)_2$/L_1	Me/Cl	-20	THF	50/50	70	**9**
7	CuTC/L_2	Me/Cl	-60	THF	49/51	75	**9**
8	CuTC/L_2	Me/Cl	-20	THF	50/50	75	**9**
9	CuI/L_2	Me/Cl	-60	THF	49/51	70	**9**
10	CuI/L_2	Me/Cl	-20	THF	50/50	70	**9**
11	$Zn(OTf)_2$/L_2	Me/Cl	-60	THF	49/51	70	**9**
12	$Zn(OTf)_2$/L_2	Me/Cl	-20	THF	50/50	70	**9**
13	CuTC/L_1	Me/Cl	-70	THF	49/51	70	**9**
14	CuTC/L_1	Me/Cl	-20	DCM	49/51	70	**9**
15	CuTC/L_1	Me/Cl	-35	Toluene	48/52	72	**9**
16	CuTC/L_1	Me/Cl	-60	THF	48.5/51.5	72	**9**
17	CuTC/L_2	Me/Cl	-60	THF	48/52	70	**9**
18	CuI/L_1	Me/Cl	-60	THF	47/53	74	**9**
19	CuI/L_2	Me/Cl	-60	THF	48/52	75	**9**
20	CuTC/L_1	Me/Cl	-40	MTBE	48.5/51.5	70	**9**
21	CuTC/ L_1	Et/Cl	-40	MTBE	49/51	69	**13**
22	CuTC/ L_1	^{i}Pr/Br	-40	MTBE	49/51	67	**14**
23	CuTC/ L_1	^{t}Bu/Cl	-40	MTBE	72/28	68	**15**
24	CuTC/ L_1	^{t}Bu/Cl	-70	MTBE	76.5/23.5	69	**15**
25	CuTC/ L_1	^{t}Bu/Cl	-70	THF	52/48	65	**15**
26	CuTC/ L_1	^{t}Bu/Cl	-70	DCM	53/47	66	**15**
27	CuTC/L_2	^{t}Bu/Cl	-70	MTBE	57/43	60	**15**
28	CuI/L_3	Me/Cl	-70	MTBE	49.2/50.8	68	**9**
29	CuI/L_3	Et/Cl	-70	MTBE	49/51	64	**13**
30	CuI/L_3	^{i}Pr/Br	-70	MTBE	49.1/50.9	64	**14**
31	CuTC/L_3	^{t}Bu/Cl	-70	MTBE	61/39	62	**15**
32	CuI/L_3	^{t}Bu/Cl	-70	MTBE	98.5/1.5	62	**15**
33	CuTC/L_3	Ph/Cl	-70	MTBE	50.5/49.4	62	**16**
34	CuTC/L_3	Benzyl/Cl	-70	MTBE	49.4/50.5	60	**17**
35	CuI/L_3	^{t}Bu/Cl	-70	DCM	70/30	58	**15**
36	CuI/L_3	^{t}Bu/Cl	-70	THF	75/25	62	**15**
37	CuI/L_3	^{t}Bu/Cl	-70	MTBE	97.9/2.1	64	**15**
38	CuI/L_3	^{t}Bu/Cl	-70	MTBE	97.9/2.1	65	**15**
39	CuI/L_3	^{t}Bu/Cl	-70	MTBE	97.8/2.2	63	**15**

HPLC: Agilent, model no.: 1260, Chiralcell OJ 250 X 4.6, 5 µm, n-Hexane, Ethanol & Acetic acid=6:4:0.1/9:1:0.001, 0.9 mL/ min, 240 nm.

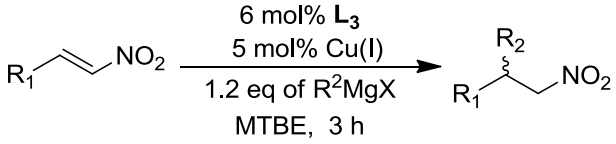
We started the screening of the catalytic system by using 6 mol% of (*S*,*S*)-isopropyl bisoxazoline ($\mathbf{L_1}$)and(*R*)-BINAP ($\mathbf{L_2}$) ligands in combination with 5 mol% of CuTC or CuI or $Zn(OTf)_2$as a metal source, 1.2 eq. of methyl magnesium halide in THF or toluene or dichloromethane and Michael acceptor **10** to obtain **9** as shown in Table 2 (entries 1 and 15)**.** No selectivity was observed in any of the experiments conducted. Undeterred with the results, we continued our efforts to understand the ligand and catalyst quantity.In a second set of experiments, we employed 20 mol% of (*S, S*)-isopropyl bisoxazoline ($\mathbf{L_1}$)& (*R*)-BINAP ($\mathbf{L_2}$) ligands in combination with 15 mol% of CuTC or CuI in THF, 1.2 eq. methyl magnesium halide in THF, Michael accepter **10** to obtain **9** as shown in Table 2 (entries 16 and 19). We did not observe anyselectivity in all the experiments but wecontinued our efforts also to understand the steric effect of Grignard reagents and solvents.In a third set of experiments ethyl, isopropyl and tert-butyl Grignard reagents were screened in ^{t}BuOMe (MTBE) or THF or CH_2Cl_2solvent by using ligand 20 mol% of (*S*,*S*)-isopropyl bisoxazoline $\mathbf{L_1}$& (*R*)-BINAP $\mathbf{L_2}$ ligands in combination with 15 mol% of CuTC. Eventually, we observed slight improvement in selectivity as shown in Table 2 (entries 23 and 24).Moreover, third set of experiments revealed that there is steric effect arising from the combination of the reagent and solvent. However, there is no major impact of $\mathbf{L_1}$ and $\mathbf{L_2}$ ligands. Optimistically, we started exploring the possibility of improving the selectivity with different class of ligands e.g. chiral ferrocenyl diphosphine ($\mathbf{L_3}$). Thus, in the fourth set of experiments we involved ligand $\mathbf{L_3}$ and keeping the reaction conditions almost similar to those in the third set.Here excellent selectivity was observed for the compound **15**with moderate yield as shown in Table 2 (entry 32).

The catalyst precursor CuI along with $\mathbf{L_1}$ or $\mathbf{L_2}$ was experimentally compared to other commonly applied Cu(I) salt e.g. CuTCand it turned out to be superior in comparison to other salts (*vide infra*). The influence of the solvent on the selectivity of the 1,4 addition was studied with the Cu(I)/$\mathbf{L_3}$catalyst. This revealed that the ethereal solvents performed better in terms of stereoselectivity. Less bulky solvent furnished the 1,4-addition product with poor selectivity whereas sterically more bulky ethers e.g. MTBE provided the best enantioselectivities (Table 2; entries 23, 24, 31, &32). Other solvents such as THF and CH_2Cl_2 led to almost *racemic* products (Table 2; entries 25, 26, 35 & 36). Eventually, MTBE as a solvent was found to be a choice for further studies. Importantly, with branched-chain and bulky Grignard reagents such as ^{t}BuMgCl a dramatic improvement in the enantioselectivity to an *er* of 98.5/1.5 was observed (Table 2; entry 32).

Considering the optimized conditions, establishing the reproducibility of this transformation was achieved by successfully conducting three consecutive batches (Table 2; entries 37, 38& 39).

Substrate scope was also explored. We employed various olefinsderived frombenzaldehyde, 4-ethoxybenzaldehyde, 4-methoxybenzaldehyde, 4-chlorobenzaldehyde, 4-flourobenzaldehyde and napthaldehyde in the1,4-addition of^{t}BuMgCl and *tert*-pentylMgCl as Grignard reagent in MTBE. Some of the substrates have rendered excellent selectivities (Table 3; entries 3,5,7 and 10).

Table3. Screening of various nitro olefins and tertiary Grignard'sby using ligand **L_3** in MTBE



S.No.	Catalyst	$R^1/R^2/X$	°C	*er (R/S) (HPLC)*	% (Yield)	Product
1	CuI/L_3	Ph/^{t}Bu/Cl	-70	*60/40*	60	**18**
2	CuI/L_3	4-EtO-Ph/^{t}Bu/Cl	-70	*77/23*	65	**19**
3	**CuI/L_3**	**4-F-Ph/^{t}Bu/Cl**	**-70**	***96.5/3.5***	**60**	**20**
4	CuI/L_3	4-MeO-Ph/^{t}Bu/Cl	-70	*71.4/28.6*	57	**21**
5	**CuI/L_3**	**4-Cl-Ph/^{t}Bu/Cl**	**-70**	***99/1***	**55**	**22**
6	CuI/L_3	Np/^{t}Bu/Cl	-70	*84.3/15.7*	58	**23**
7	**CuI/L_3**	**6Mn/^{t}Pentyl/Cl**	**-70**	***99/1***	**48**	**24**
8	CuI/L_3	Np/^{t}*Pentyl* /Cl	-70	*87.8/12.2*	50	**25**
9	CuI/L_3	4-MeO-Ph/^{t}*Pentyl* /Cl	-70	*73/27*	52	**26**
10	**CuI/L_3**	**4-F-Ph/^{t}*Pentyl* /Cl**	**-70**	***96.2/3.8***	**45**	**27**

HPLC: Agilent, model no.: 1260, Chiralcell OJ 250 X 4.6, 5 µm, n-Hexane, Ethanol & Acetic acid=9:1:0.001, 0.9/9.5:0.5:0.001; 0.9 mL/ min, 240 nm.

As evident in the various reactions, the chiral ferrocenyl diphosphine ligand **L_3** afforded best enantioselectivity, which can be envisaged by considering the proposed catalytic cycle outlined in Figure 3.

The working hypothesis may involve the transfer of an alkyl ligand from the organometallic reagent to the Cu(I).

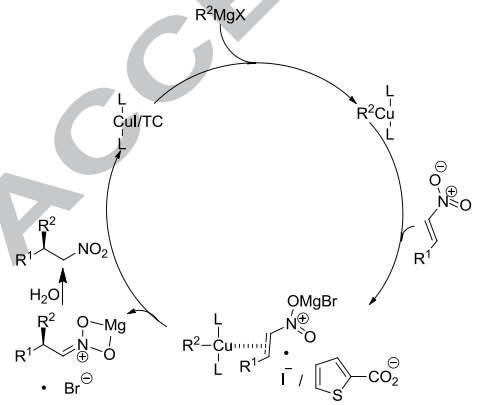


Figure 3. Proposed C-C bond formation triggered by copper catalyzed conjugate addition of Grignard reagent

Subsequent complexation of the –MgBr byproduct with the nitro groupand formation of the π−complex of the alkylcopper species with the C−C double bond of the activated olefin can result in the formation of the heterobimetallic complex. Subsequent alkyl transfer from the copper species to the substrate can generate the magnesium nitronate. The enantioselectivity of the overall transformation is presumed to be determined by the alkyl transfer in a preferential manner. The resulting chiral magnesium nitronatecan finally decompose to afford 1,4-addition product.

Assuming the heterobimetallic species and significant steric hindrance involved in this transformation we propose a transition state where an addition of R^2 group occurred *anti* to the plane in which hydrogen is placed affording *R* configured product. The transition state plausibly indicates that apart from chiral ligand (**L_3**), the size of the substituents (R^1) in nitroolefin substrate in combination with the incoming group (R^2) imparts in this stereoselective transformation as shown in Figure 4.

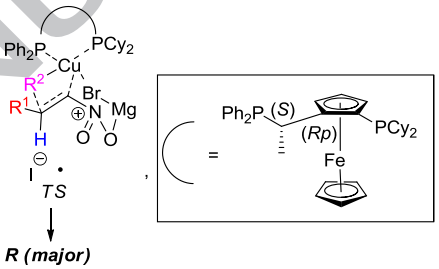


Figure 4. Proposed transition state

Resulting nitroalkanes(**15** and **20**) were converted to corresponding carboxylic acids **28**and**29**by using *Nef* reaction conditions(Figure 5) in good yields (70% & 64%) as well as with acceptable enantioselectivities (*ee* 95.8%, & 93%).

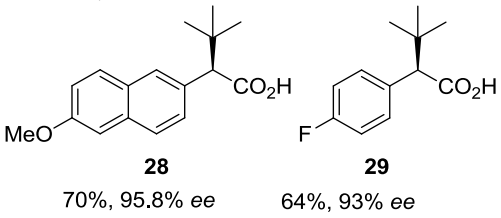


Figure 5. Structure of acid derivatives **28** and **29**

Table4. Conversion of nitro alkanes **15** and **20** to carboxylic acid derivatives **28**and**29** by using *Nef* reaction conditions

S.No.	Input	°C	*er (R/S) (HPLC)*	% (Yield)	$[\alpha]_D^{25}$	Product
1	15	25	*97.9/2.1*	70	-77.5	**28**
2	20	25	*96.5/3.5*	64	-35	**29**

HPLC: Agilent, model no.: 1260, (*S,S*) whelk-01 250 X 4.6 mm (5µ); n-Hexane, Ethanol & Acetic acid=80:20:0.5.

In conclusion, we demonstrated the first enantioselective 1,4-addition of Grignard reagent to nitroolefin and novel *racemic* synthesis of naproxen (which was further resolved into the corresponding enantiomers) by employing nitro aldol followed by 1,4-addition and Nef reaction.

Acknowledgement

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Supplementary Material

Experimental procedures and compound characterization data are described in supplementary material.

DRL-IPD Communication number: **IPDO IPM – 00282**

The chiral HPLC chromatograms were recorded on Agilent Model No.: 1260 by Chiralcell OJ 250 X 4.6, 5 µm, mobile phase: n-Hexane, Ethanol & acetic acid (6:4:0.001)/ (9:1:0.001)/(9.5:0.5:0.001).

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1. http://www.rxlist.com/cgi/generic/naproxsod.htm.

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