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Combination Amine and Metal Cascade Catalysis

"COMBICAT"

COMBINATION AMINE AND METAL CASCADE CATALYSIS & ORGANOCATALYTIC DESYMMETRISATION OF PROCHIRAL CYCLOHEXANONES VIA INTRAMOLECULAR MICHAEL ADDITIONS

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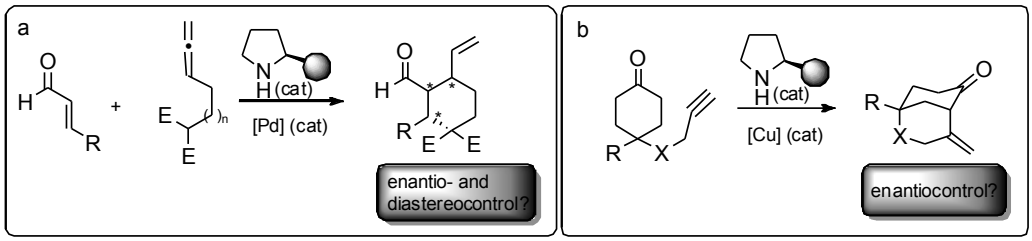
1) WORK PROGRESS AND ACHIEVEMENTS DURING THE PERIOD:

A. *COMBINATION AMINE AND METAL CASCADE CATALYSIS*

A.1 INTRODUCTION

Our proposal is aimed to develop new and synthetically powerful cyclisation cascades using combinations of amine organocatalysts and transition metal catalysts. Carefully chosen combinations of these catalysts should allow aldehyde and ketone functionality to be activated



Scheme1: Concept of cyclisation cascade using combination of amine organocatalysts and metal catalysts

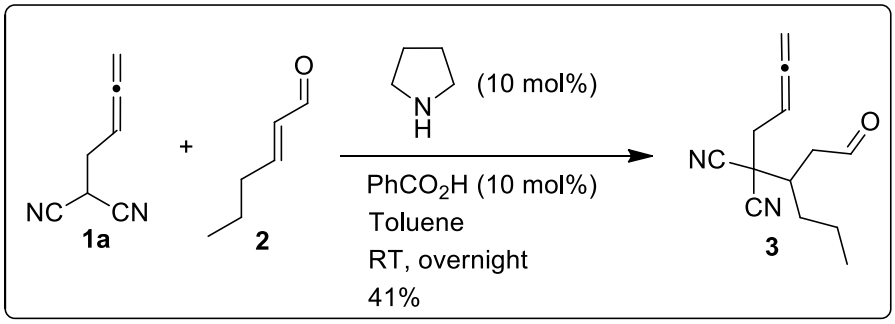
through conversion to a transient enamine intermediate that is then poised to attack the transition metal-activated allene (Scheme 1a) and alkyne functionality (Scheme 1b). This concept can be extended to new annulation methodology when enal Michael acceptors are employed (Scheme 1a). In this case carbon acids tethered to allene functionality can undergo an initial Michael addition under iminium ion (LUMO lowering) activation using amine organocatalysts and the generated enamine intermediate is then poised to attack the transition metal-activated allene group. Furthermore, through use of effective single enantiomer organocatalysts it is possible to render this powerful annulation reaction asymmetric (Scheme 1a and 1b).

A.2 RESULTS

A.2.1 *Development of new enantioselective allene cyclizations through combination iminium, enamine and metal catalysis*

A) Enantionselective Michael Addition:

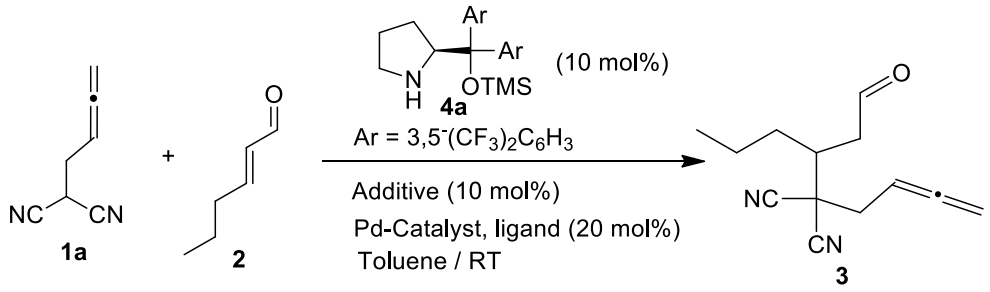
We first decided to find the appropriate amine and metal catalyst which can effectively and also enantioselectively catalyze the first step i.e. the Michael addition step. We started our experiment with 2-(buta-2,3-dien-1-yl)malononitrile **1a** as nucleophile and (*E*)-hex-2-enal **2** as Michael acceptor. **1a** and **2** were treated with pyrrolidine and benzoic acid in toluene at room temperature overnight. Michael adduct **3** was obtained in 41% yield (Scheme 2).



Scheme 2: Initial Michael addition reaction

This result encouraged us to investigate the enantioselective version of the reaction. We first took Jorgensen catalyst **4a** as an organocatalyst and screened different palladium catalysts. Results are depicted in Table 1. Palladium(II) acetate in presence of benzoic acid produced **3** in only 25% yield (table1, entry 1). Addition of triphenylphosphine gave only messy reaction mixture (table 1, entry 2). Similarly $Pd_2(dba)_3$ yielded **3** in 22% yield whereas $Pd(PPh_3)_4$ gave messy reaction mixture (table1, entry 3 and 4). $PdCl_2$(dppf) proved to be very effective for this reaction. It afforded 71% of product in presence of benzoic acid (table 1, entry 5) and 92% in absence of it (table1, entry 6).

Table 1: Palladium catalyst screening for Michael addition

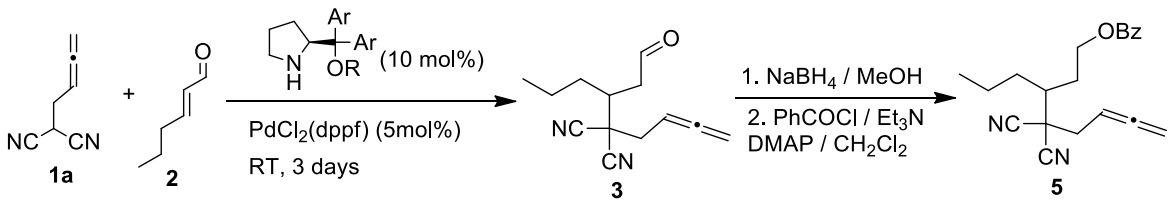


Entry	Pd-Catalyst	Ligand	Additive	Time	Result/Yield (%)

1	$Pd(OAc)_2$	---	$PhCO_2H$	48 h	25
2	$Pd(OAc)_2$	PPh_3	$PhCO_2H$	48 h	Messy
3	$Pd_2(dba)_3$	---	$PhCO_2H$	48 h	22
4	$Pd(PPh3)_4$	---	$PhCO_2H$	48 h	Messy
5	$PdCl_2(dppf)$	---	$PhCO_2H$	24 h	71
6	$PdCl_2(dppf)$	---	---	72 h	92

After having this excellent yield with $PdCl_2(dppf)$ for Michael addition step, we were interested to see the enantioselectivity of the reaction using various Jorgensen catalysts. The resulting aldehyde was converted to first alcohol using sodium borohydride and then to benzoate ester using benzoyl chloride and triethylamine for HPLC analysis. Results are summarized in Table 2. As mentioned before (table 1) the yield of the reaction with organocatalyst **4a** was excellent, HPLC analysis shows that ee is also excellent (89%, entry 1, table 2). All the other amine catalysts also produced good to excellent yield and selectivity (table 2). The best yield (92%) was obtained when R is trimethylsilyl group (**4a**) and the best ee (95%) was obtained as when R is bulky tert-butyldimethylsilyl group (**4e**, table 2, entry 5).

Table 2: Palladium catalysed enantioselective Michael addition

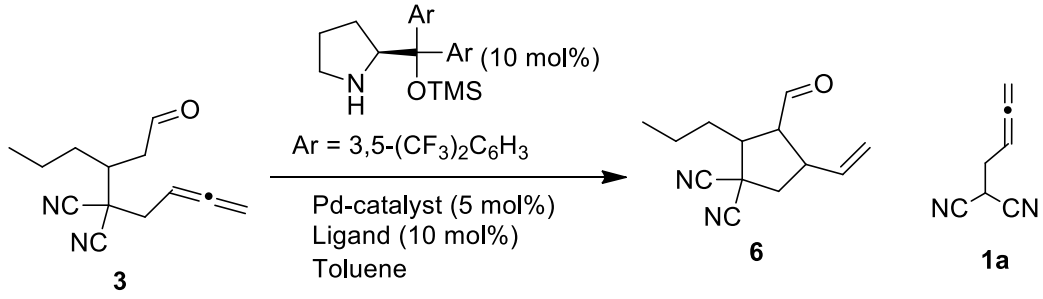


Entry	R	Ar	Yield (%)	ee (%)
1	TMS	3,5-$(CF_3)_2C_6H_3$(**4a**)	92	89
2	Me	3,5-$(CF_3)_2C_6H_3$(**4b**)	90	88
3	TIPS	3,5-$(CF_3)_2C_6H_3$(**4c**)	65	94
4	TIPS	2-Naphthyl(**4d**)	92	78
5	TBDMS	3,5-$(CF_3)_2C_6H_3$(**4e**)	78	95
6	TBDMS	3,5-$(CH_3)_2C_6H_3$(**4f**)	90	75
7	TBDMS	C_6H_5(**4g**)	87	75

B) Cyclization:

After having this excellent result with respect to both yield and enantioselectivity for Michael addition step the obvious move was to find the right catalyst for cyclization step. Variuos palladium catalysts were screened for enantioselective cyclization of Micheal adduct **3** using **4a** as an organocatalyst (table 3). Our first choice was $PdCl_2$(dppf) as this gave good yield and selectivity for the first step. But treatment of **3** with $PdCl_2$(dppf) and **4a** in toluene at 100 ^oC for 14 h did not produce cyclized product **6** at all (entry 1). Instead, it gave allene **1a** back as a result of retro Michael addition. Unfortunately, all other palladium catalysts used was unable to deliver any cyclized product (entry 2-8). $[AllylPdCl]_2$/dppf, $Pd(OAc)_2$, $Pd_2(dba)_3$/dppe, and $Pd(dppe)_2$ gave only messy reaction mixture (entry 2-5) whereas $Pd(PPh_3)_4$ decomposed aldehyde 3 (entry 6). $Pd(CH_3CN)_2Cl_2$ and $Pd(PPh_3)_2Cl_2$ also proved to be not effective and gave only staring material back (entry 7-8).

Table 3: Palladium catalyst screening for cyclization

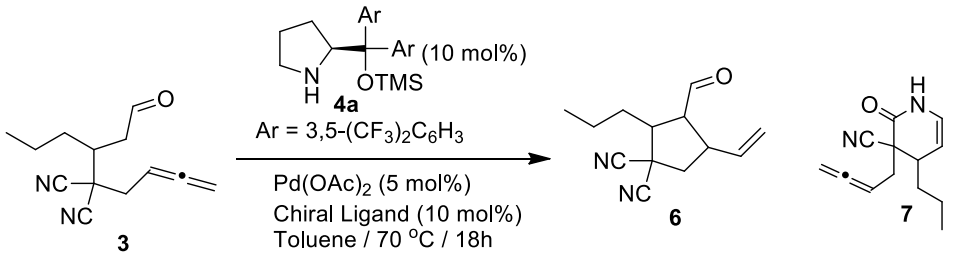


Entry	Pd-catalyst	Ligand	Temperature	Time	Result/Product
1	$PdCl_2$(dppf)	---	100 ^oC	14 h	1
2	$[AllylPdCl]_2$	dppf	70 ^oC	12 h	messy
3	$Pd(OAc)_2$	---	70 ^oC	24 h	messy
4	$Pd_2(dba)_3$	dppe	RT	36 h	messy
5	$Pd(dppe)_2$	---	70 ^oC	24 h	messy
6	$Pd(PPh_3)_4$	---	70 ^oC	24 h	decomposed
7	$Pd(CH_3CN)_2Cl_2$	---	100 ^oC	14 h	no reaction
8	$Pd(PPh_3)_2Cl_2$	---	100 ^oC	14 h	no reaction

We then thought of employing chiral phosphine ligand which might trigger the reaction. Cyclization of **3** was investigated with **4a** as an organocatalysis, $Pd(OAc)_2$ as a metal catalyst and various chiral phosphine ligand such as Jesiphos, Walphos etc. (Table 4). Treatment of **3** with **4a**, $Pd(OAc)_2$ and Jesiphos (SL-J001-1) in toluene at 70 ^oC for 18 h provided no desired product, but **7** in 71% yield with dr 1:1 (table 4, entry 1). Messy reaction mixture was resulted when Walphos (SL-W001-1) was employed (table 4, entry 2). Similarly no desired product was obtained when Mandiphos (SL-M001-1), Taniaphos (SL-T001-1) and SL-A101-1 were used. Only 7 was

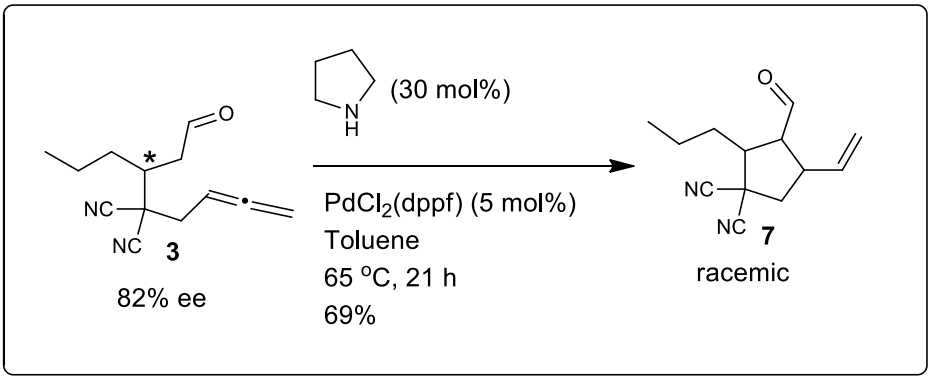
produced in poor yield (table 4, entries 3-5).

Table 4: Chiral ligand screening



Entry	Chiral Ligand	Result/Product	Yield(%)	dr
1	SL-J001-1	7	71	1:1
2	SL-W001-1	messy	---	…
3	SL-M001-1	7	29	1:5
4	SL-T001-1	7	10	…
5	SL-A101-1	7	21	1:5

As the palladium catalyst screening and chiral ligand screening were unsuccessful, we thought that steric bulk of chiral amine is preventing the cyclization. So we wanted to see whether chirality obtained in the Michael addition step can be transferred to the cyclization step using a achiral secondary base such as pyrrolidine. Enantiorich substrate **3** (82% ee) was treated with 30 mol% pyrrolidine and 5 mol% of $PdCl_2$(dppf) in toluene at 65 ^oC for 21 hour (scheme 2). Although the desired cyclized product **7** was obtained in only one diastereomeric form, to our surprise HPLC analysis of benzoate ester of **7** was found racemic. So chirality is being lost during the reaction. This can only be possible if retro Michael products are forming during the reaction as we already observed (table 3, entry 1).

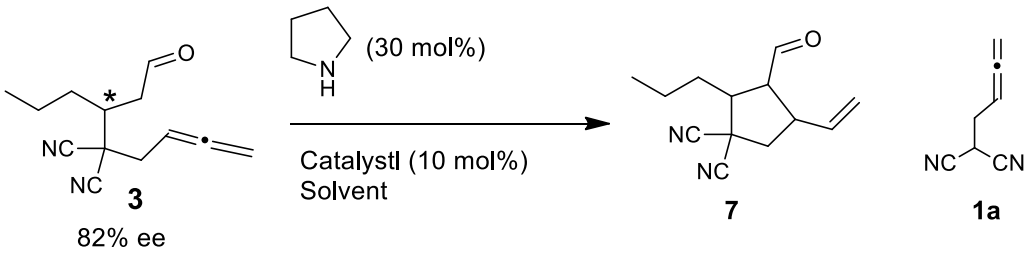


Scheme 2: Examination of chirality transfer for cyclization

To stop the retro Michael reaction we decided to try other metal catalysts such as Au, Pt as they

are also known to activate allene functionality (table 5). $PPh_3AuCl/AgSbF_6$ gave only retro Michael product allene **1a** even at room temperature in toluene and chloroform (table 5, entries 1 and 2). No reaction was found without pyrrolidine (table 5, entry 3). Changing the silver salt (AgOTf) did not work, only retro Michael reaction occurred (table 5, entry 4). Similarly, reaction with $AuCl_3$ and $PtCl_2$ provided no desired product but allene **1a** (table5, entries 5 and 6).

Table 5: Metal catalyst screening for cyclization

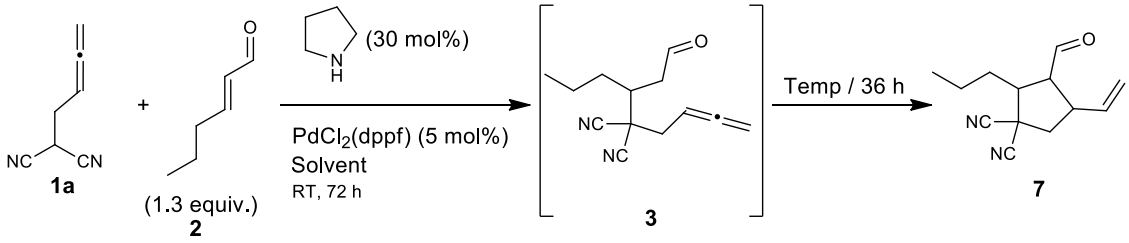


Entry	Catalyst	Solvent	Temperature	Time	Result/Product
1	$PPh_3AuCl/AgSbF_6$	Toluene	RT	13 h	1a
2	$PPh_3AuCl/AgSbF_6$	$CHCl_3$	RT	14 h	1a
3	$PPh_3AuCl/AgSbF_6$ (without pyrrolidine)	$CHCl_3$	60 ^oC	14 h	No reaction
4	$PPh_3AuCl/AgOTf$	CH_2Cl_2	40 ^oC	10 h	1a
5	$AuCl_3$	Toluene	65 ^oC	20 h	1a
6	$PtCl_2$	Toluene	65 ^oC	20	1a

C) Cascade Reaction:

We then examined the cascade reaction i.e. Machael addition followed by cyclisation in one pot (table 6). Allene **1a** was subjected to react with aldehyde using pyrrolidine as a base and $PdCl_2$(dppf) as metal catalyst in different solvent at room temperature. When Michael addition is complete (72 h) the reaction mixture was heated up for cyclization. Reaction in toluene and chloroform afforded product in 30% and 25% yield respectively (table 6, entries 1 and 3). Diastereomeric ratio in both cases was nearly 10:1. Reaction in CH_2CL_2 and THF produce only traces amount of product (table 6, entries 2 and 4) whereas no reaction was observed in 1,4-dioxane (table 6, entry 5).

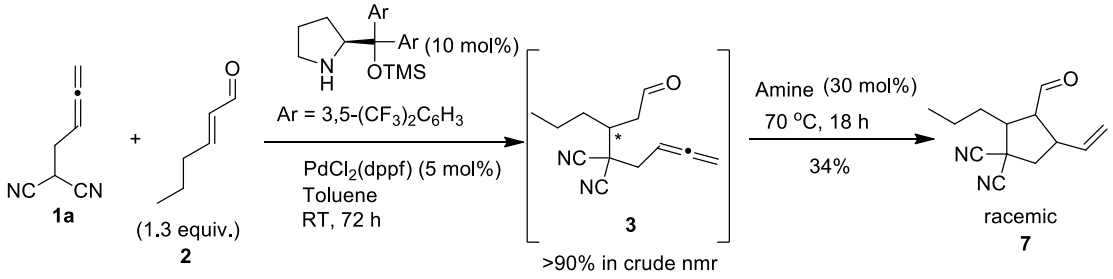
Table 6: Solvent screening for Cascade reaction



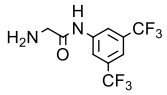
Entry	Solvent	Temperature	MA (conversion % in crude nmr)	Temperature	Result/Cyclization (yield)
1	Toluene	RT	>90	65 ^{o}C	30 %
2	CH_2Cl_2	RT	>90	50 ^{o}C	traces
3	$CHCl_3$	RT	>70	50 ^{o}C	25 %
4	THF	RT	>90	50 ^{o}C	traces
5	1,4-Dioxane	RT	>90	50 ^{o}C	no reaction

After having this result we performed the cascade reaction using chiral amine catalyst for Michael addition and different achiral amine, proline and its amide derivative for cyclization. Allene **1** was treated with aldehyde **2** in presence of **4a** (10 mol%) and $PdCl_2$(dppf) (5 mol%) in toluene and the reaction mixture was stirred at room temperature for 3 days. Achiral amine was then added to the reaction mixture and stirred at 70 ^{o}C (table 7). Product **7** was obtained in 34% yield when pyrrolidine was used, but unfortunately it was found to be racemic (table 7, entry 1). Benzyl amine and N^1,N^1-dimethylethane-1,2-diamine failed to produce the desired product (table 7, entries 2 and 3), whereas Glycine and its amide gave only retro Michael product (table 7, entries 4 and 5).

Table7: organocatalyst screening for cyclization in cascade reaction:



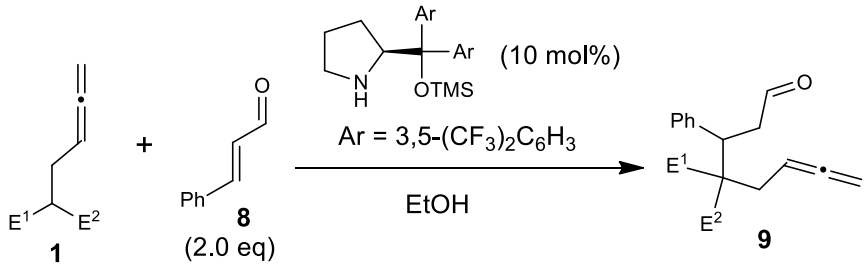
Entry	Amine	Time	Result/Product	Yield (%)/ee
1	Pyrrolidine	18 h	7	34/racemic
2	Benzylamine	14 h	messy	…
3	N^1,N^1-dimethylethane-1,2-diamine	14 h	polymer	…
4	Glycine	14 h	1	…

5		14 h	1	…

D) Miacheal addition with other allenes:

Since the retro Michael reaction is responsible for the loss of chirality, we decided to replace cyano group by less electron withdrawing group i.e., ester group. Allene derived from the dimethylmalonate was first used for Michael addition. But allene **1b** failed to react with cinnamaldehyde in presence of **4a** in ethanol solvent even at 50 ^{o}C (table8, entry 1). So we had to keep one cyano group in allene substrate to make the proton acidic enough to be abstracted by the pyrrolidine base **4a.** So we synthesized **1c** and subjected to react with cinnamaldehyde in presence of **4a**. The reaction worked well even at as low as 0 ^{o}C for 4 days affording product **9c** in 89% yield, but unfortunately with dr 1:1 (table 8, entry 2). Then the reaction was performed with $PdCl_2$(dppf). Similarly, yield obtained was very good (85%), but with no diastreoselectivity (dr 1:1) (table 8, entry 3).

Table 8: Michael addition reaction with other allenes



Entry	Substrate	Pd-Cat	T/^{o}C	Time	Result/Product	Yield (%)	dr
1	E^1=E^2 = CO_2Me (**1b**)	…	50	24 h	No reaction	…	…
2	E^1= CN, E^2= CO_2tBu (**1c**)	…	0	4 days	9c	89	1:1
3	E^1= CN, E^2= CO_2tBu (**1c**)	$PdCl_2$(dppf) (5 mol%)	0	4 days	9c	85	1:1

A.2.2 ***Development of new asymmetric desymmetrization through combination iminium, enamine and metal catalysis via alkyne cyclization***

We chose compound **10** for our investigation because the product **11** which can be obtained via asymmetric desymmetrization is very interesting as this framework is present in immunosuppressant FR901483 (1) isolated from the fermentation broth of the *Cladobotryum* species (Figure 1).

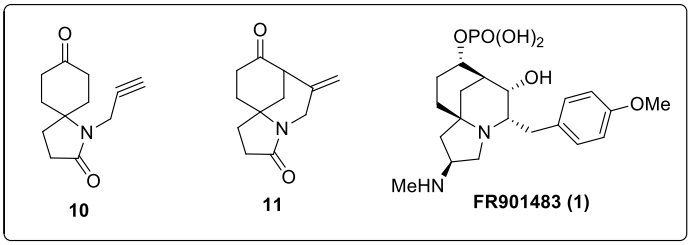
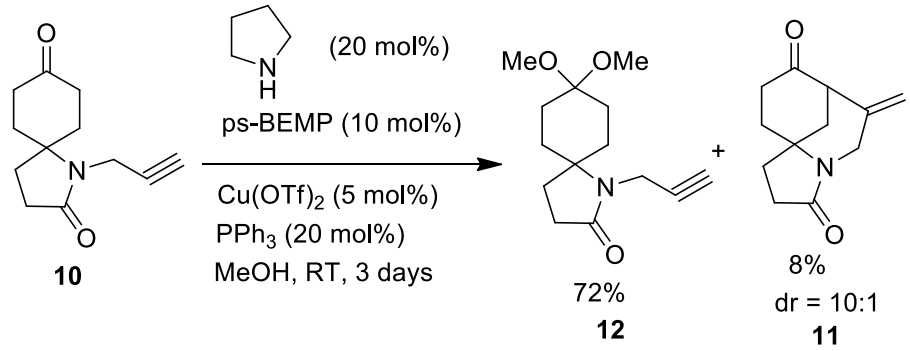


Figure 1: Significance of our asymmetric desymmetrization

A) **Solvent screening**

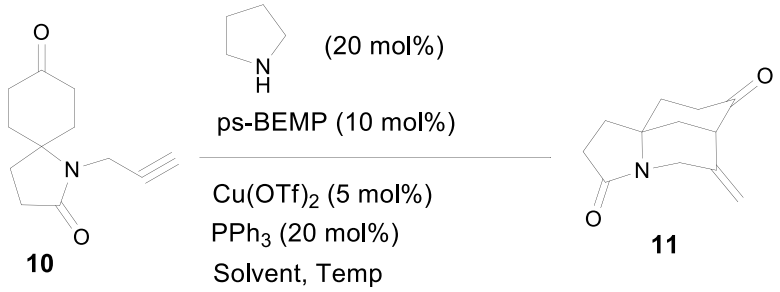
We first studied the reaction using achiral pyrrolidine, ps-BEMP, $Cu(OTf)_2$ as metal salt and PPh_3 as ligand in Methanol solvent. After stirring at RT for 3 days, we obtained only 8% of the desired product **11** together with 72% of dimethyl ketal derivative **12** of the starting material **10**.



Scheme 3: Initial experiment with achiral base

This result encouraged us for solvent screening with various aprotic solvents. Reaction in DMF at 70 ^{o}C afforded product in satisfactory 79% yield (table 9, entry 1). DCM, toluene and chloroform proved to be not effective for this reaction; they produced only traces of product (table 8, entries 3,4 and 7). Use of THF, DMSO and CH_3CN also delivered product in good yield, but a bit lower than DMF (table 8, entries 2,5 and 6). We wanted to see whether ps-BEMP is necessary at all for the reaction. And the reaction was performed without ps-BEMP in DMF solvent. Yield was increased up to 90 % after stirring the mixture at 70 ^{o}C for 20 h (table 8, entry 8).

Table 8: Solvent screening for desymmetrization



Entry	Solvent	Additive	Temp	Time	Result/Yield (%)
1	DMF	ps-BEMP	70 ^{o}C	12 h	79
2	THF	ps-BEMP	50 ^{o}C	38 h	60
3	CH_2Cl_2	ps-BEMP	50 ^{o}C	38 h	traces
4	Toluene	ps-BEMP	70 ^{o}C	24 h	traces
5	DMSO	ps-BEMP	70 ^{o}C	18 h	68
6	CH_3CN	ps-BEMP	70 ^{o}C	18 h	61
7	$CHCl_3$	ps-BEMP	60 ^{o}C	38 h	traces
8	DMF	---	70 ^{o}C	20 h	90

B) **Organocatalysts Screening**

After having the right solvent we have done a thorough amine catalyst screening. Various types of chiral amine catalysts have been synthesized for this purpose and listed in figure 2.

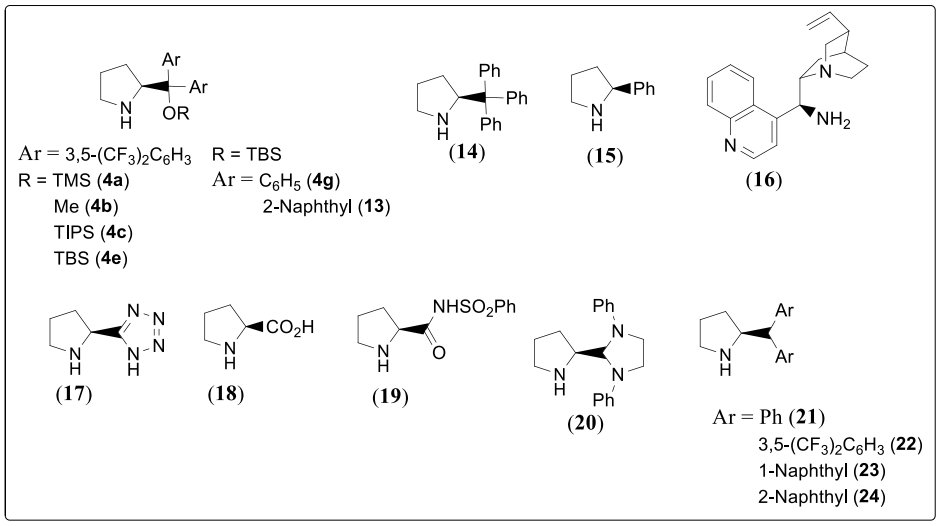
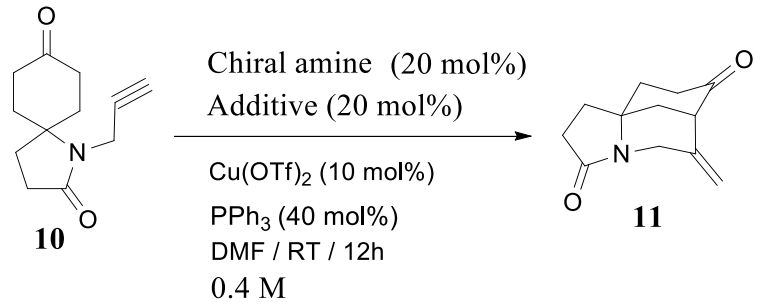


Figure 2: List of organocatalysts used for asymmetric desymmetrization

The screening was performed with substrate **10** using $Cu(OTf)_2$ as metal catalyst in DMF solvent. Results are depicted in table 9. Jorgensen catalysts **4a**, **4c**, **4e**, **4g** and **13** failed to deliver any product (table 9, entries 1-3 and 5-6). Catalyst **4b** gave only 30% product which was found racemic (table 9, entry 4). Catalyst **14** with three phenyl substituents provided 11% of racemic product (table9, entry 7). So we thought it is the steric bulk which is preventing the reaction to occur. We then used **15** for the reaction. Interestingly it gave product in 52% yield, but the ee was low (34%) (table 9, entry 8). We then switched to cinchonine derivative **16** for the reaction. But it only gave traces of product after stirring at 125 ^{o}C for 30 h (table 9, entry 9). Addition of benzoic acid and TFA with 16 did not help (table 9, entries 10-12). We studied the reaction without any

organocatalyst. After stirring at 110 ^{o}C for 42 h **11** was obtained in 38% yield (table9, entry 13). We have observed that at below 110 ^{o}C the reaction did not occur. This result says that the reaction proceeds via ene reaction of the enol form at 110 ^{o}C. So we need to keep the reaction temperature below 110 ^{o}C to get enantioselectivity. Use of **17** as a chiral base provided diminished yield (24%), but higher ee (46%) than its phenyl analogue (table 9, entry 14). Then we tried proline **18** and its sulfonamide derivative **19**: proline gave 39% yield and 12% ee, whereas its sulfonamide derivative failed to give any product at below 110 ^{o}C, and after stirring at 125 ^{o}C for 50 h it produced only 10% of product with no enantioselectivity as expected (table 9, entries 15-16) . Surprisingly, **20** was unable to give any product even at 110 ^{o}C (table9, entry 17). After that we tried amine 21-24. Treatment of **10** in presence of **21** in DMF at 90 ^{o}C for 15 h delivered product in 45% yield and 64% ee. Increasing the steric bulk by replacing phenyl group with 3,5-bis(trifluoromethyl)phenyl group (**22**) decreased the reaction rate (144 h) and also the yield (28%), but slightly increased enentioselectivity (67% ee). Similar result was observed in case of 1-naphthyl substituent (**23**). However, in case of 2-naphthyl substituent (**24**), better yield (51%) was obtained with lower ee (54%) (table 9, entries 18-21). When benzoic acid was used as an additive with catalyst 21, yield was increased up to 61%, but enantioselectivity was decreased (table9, entries 22-24).

Table 9: Screening of organocatalysts for asymmetric desymmetrization



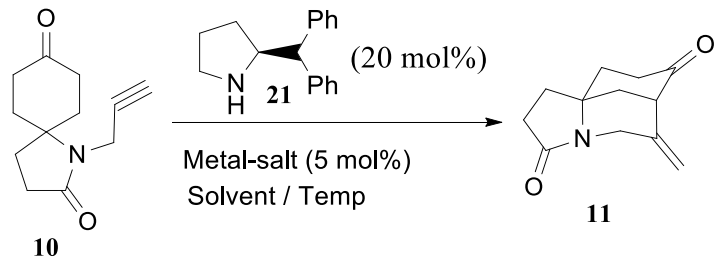
Entry	Chiral Amine	Additive (mol%)	T/ ^{o}C	t/h	Result/Yield(%)	ee(%)
1	4a	…	110	5.5	decompsoed	…
2	4c	…	110	19	traces	…
3	4e	…	110	19	messy	…
4	4b	…	110	23.5	30	0
5	4g	…	110	19 h	messy	…
6	13	…	110	19	traces	…
7	14	…	110	72	11	0
8	15	…	70	65	52	34
9	16	…	125	30	traces	…
10	16	$PhCO_2H$	125	30	messy	…

		(20)				
11	16	$PhCO_2H$ (40)	110	15	messy	…
12	16	TFA (40)	70	22	Messy	…
13	…	…	110	42	38	0
14	17	…	110	53	24	46
15	18	...	90	37	39	12
16	19	…	125	50	10	0
17	20	…	110	24	No reaction	…
18	21	…	90	15	45	64
19	22	…	90	144	28	67
20	23	…	90	144	21	68
21	24	…	90	120	51	54
22	21	$PhCO_2H$ (5)	90	96	61	54
23	21	$PhCO_2H$ (10)	90	120	52	59
24	21	$PhCO_2H$ (20)	90	120	49	59

C) **Metal Catalyst Screening**

After finishing the organocatalyst screening we attempted to screen different other metals as a catalyst. $AuCl(PPh_3)$ was used with different silver salt. AgOTf was not effective whereas $AgNTf_2$ and $AgSbF_6$ yielded 28% and 25% product with 53% ee (table 10, entires 1-3). $AuCl_3$ and AgOTf alone didn't react (entries 4-5) and $Pd(PPh_3)_4$ and $PtCl_2$ decompsed the starting material (table 9, entries 6-7).

Table 9: Metal catalyst screening



Entry	Metal Salt	Solvent	T/ ^oC	t/h	Yield	ee
1	$AuCl(PPh_3)$/AgOTf	DCE	90	44	traces	…

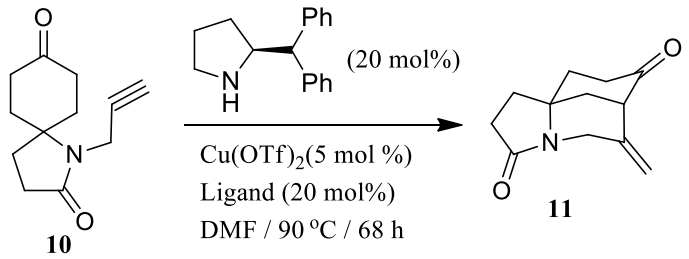
2	$AuCl(PPh_3)/AgNTf_2$	DCE	85	24	28	53
3	$AuCl(PPh_3)/AgSbF_6$	DCE	85	24	25	53
4	$AuCl_3$	DCE	85	54	NR	…
5	AgOTf	DCE	85	44	NR	…
6	$Pd(PPh_3)_4$	Toluene	RT	12	decomposed	…
7	$PtCl_2$	Toluene	110	20	decomposed	…

D) **Ligand Screening**

To increase the enentioselectivity we tried different phosphine ligand with **21** as amine catalyst. But none of them could increase the enantioselectivy and yield. Results are depited in Table **10**.

Table 10: Ligand Screening

Entry	Ligand	Result / Yield (%)	ee
1	DPPE	NR	…
2	DPPF	40	46
3	2-(dicyclohexylphosphino)-1,1'-biphenyl	messy	…
4	S-BINAP	42	46
5	R-T-BINAP	39	52



A.3 CONCLUSION:

Unfortunately enantioselectivity was not obtained more than 67%. So we decided to change the substrate. Alkyne group was replaced by *α,β* -unsaturated ester.

B. *ORGANOCATALYTIC DESYMMETRISATION OF PROCHIRAL CYCLOHEXANONES VIA INTRAMOLECULAR MICHAEL ADDITIONS*

We chose substrate of type **X** (Figure 1) as a model system for asymmetric desymmtrization; its precursor was known and accessible on scale and a cross metathesis would provide a point of diversification if the desymmetrization was successful.

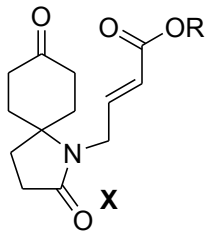
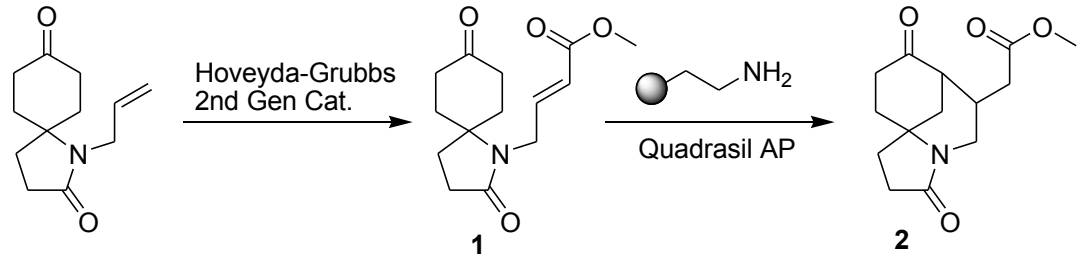


Figure 1: Substrates for asymmetric desymmetrization

B.1 Results & Discussion:

By good fortune attempted purification of **1** from ruthenium residues, remaining from the cross metathesis reaction, with quadrasil AP resulted in a good yield of the cyclized product (**Scheme 1**).



Scheme 1: Attempted purification lead to cyclizasion

B.1.1 *Catalyst Screen*:

These both validated our concept and provided a basis for an initial primary chiral amine screen even though uses less profusely in organocatalysis.

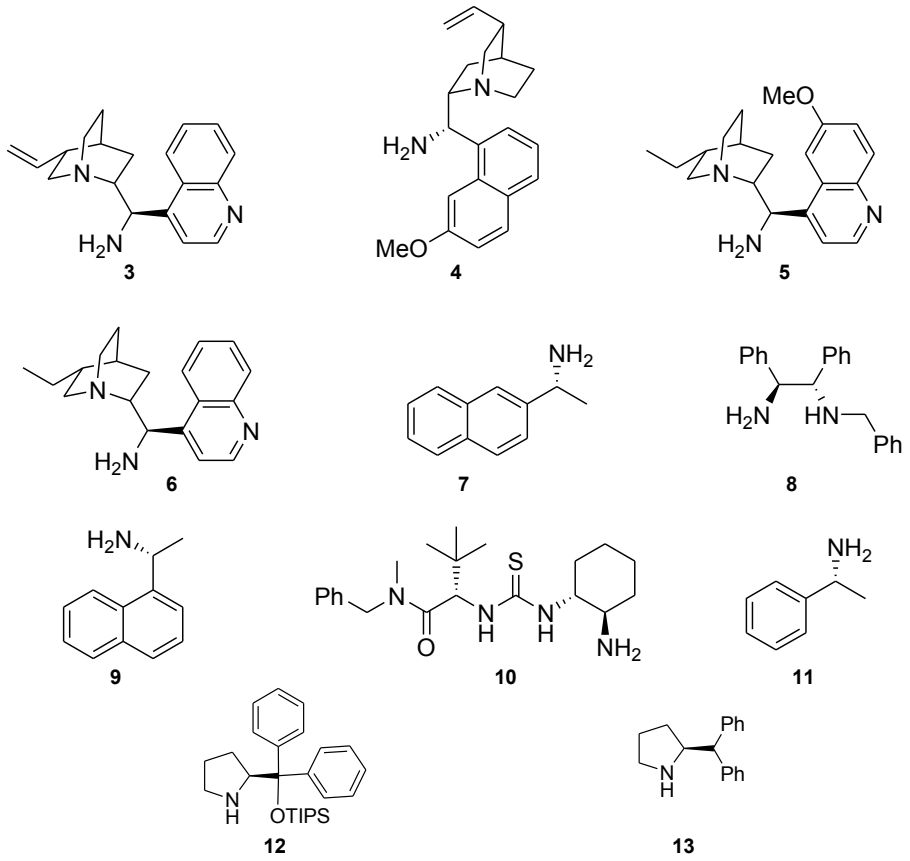


Figure 2: List of amine catalysts used

A range of primary amines (20 mol% for convenience sake 1:1 with benzoic acid co-catalyst) were screened in the model reaction using dichloromethane as solvent. Pleasingly moderate to high enantioselectivities with high diastereoselectivities and good reactivity was seen across the range of primary amines screened, with Jacobsen's catalyst being the best. A crosscheck with secondary amines gave no reactivity confirming primary amines were superior (Table 1).

Table 1: Catalyst screen

Catalyst	Time	Yield [%]	dr [%]	ee* [%]
3	7 days	72	87:13	-49/85
4	7 days	63	91:1	46/80
5	7 days	66	90:10	73/53
6	7 days	70	82:18	-51/-52
7	3.5days	70	98:2	70
8	7 days	72	94:6	34/72
9	7 days	79	94:6	80/50
10	26hrs	95	97:3	90/20

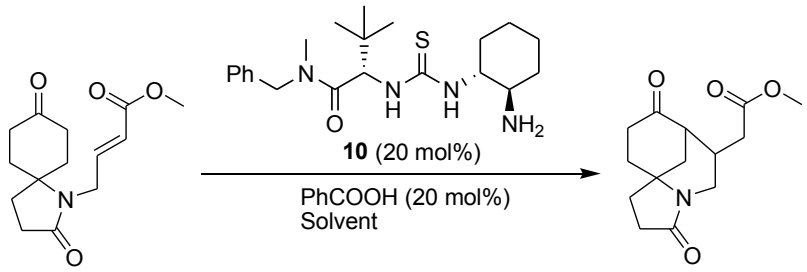
11	7days	80	>98:2	-66
12	7 days	No reaction	--	--
13	7 days	No Reaction	--	--

*Major/ minor. 20mol% Catalyst, 20mol% benzoic acid. DCM , RT

B.1.2 *Solvent Screen*:

A quick solvent screen (**Table 2**) showed that DCM and Chloroform gave the best ee & dr.

Table 2: Solvent screen

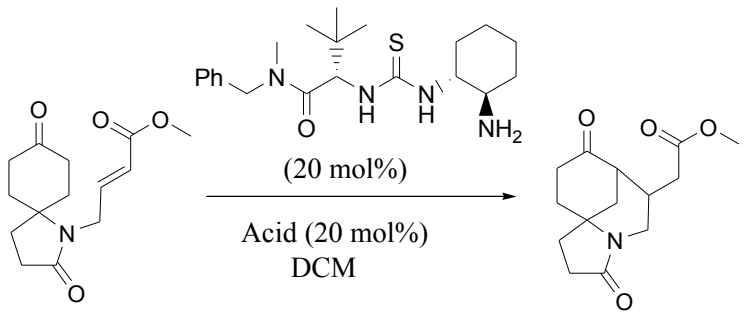


Solvent	Temp	Time	Yield (%)	Dr	ee (major/minor, %)
CH_2Cl_2	rt	26 h	95	97 : 3	90 / 20
$CHCl_3$	rt	28 h	89	97 : 3	90 / 4
Toluene	rt	32 h	78	77 : 23	44 /55
Et_2O	rt	32 h	75	89 : 11	12 / 55
TBME	rt	32 h	79	80 : 20	8 : 69
MeOH	60 ^oC	72 h	72	90 : 10	Rac / 15

B.1.3 *Acid Cocatalyst Screen:*

An acid cocatalyst screen using Jacobsen's catalyst as the primary amine revealed benzoic acid and para nitrophenol to be best (**Table 3**); the former was adopted for the remainder of this work due to the considerably faster reaction times.

Table 3: Cocatalyst Screen



Acid	Temp	Time	Yield (%)	dr	ee (major/minor, %)
$PhCO_2H$	RT	26 h	95	97:3	90/20
4-F-C_6H_4COOH	RT	65 h	84	97:3	88/13
4-NO_2-C_6H_4COOH	RT, 40 ^oC	48 h, 50 h	82	96:4	88/6
CH_3CO_2H	RT	40 h	89	96:4	89/9
CF_3COOH	RT, 40 ^oC	48 h, 85 h	75	94:6	88/30
*p*TSA	RT, 40 ^oC	48 h, 48 h	NR	…	…
4-NO_2-C_6H_4-OH	RT	72 h	84	96:4	92/18
(*S*)-BINOL	RT	48 h	90	97:3	86/20
(*R*)-BINOL	RT	48 h	86	96:4	88/18

B.1.4 *Catalyst Loading*:

Further optimisation showed that the Jacobsen's catalyst and benzoic acid loading could be lowered to 5mol % and 1.25 mol % respectively. The longer reaction times associated with the lower catalyst loadings were overcome by warming the reaction to 45 ^oC with no effect on the ee or dr (**Table 4**).

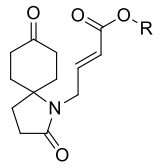
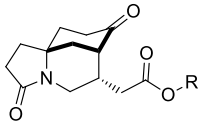
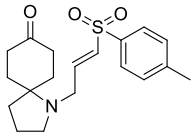
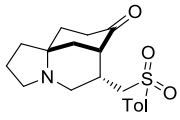
Table 4: Catalyst Loading

Jacobsens catalyst [mol%]	Benzoic Acid [mol%]	Temp [^oC]	Time	Yield [%]	Dr [%]	ee(major) [%]
20	20	25	26 h	95%	97:3	90
5	1.25	45	36 h	88%	97:3	92

B.1.5 *Scope of the Reaction:*

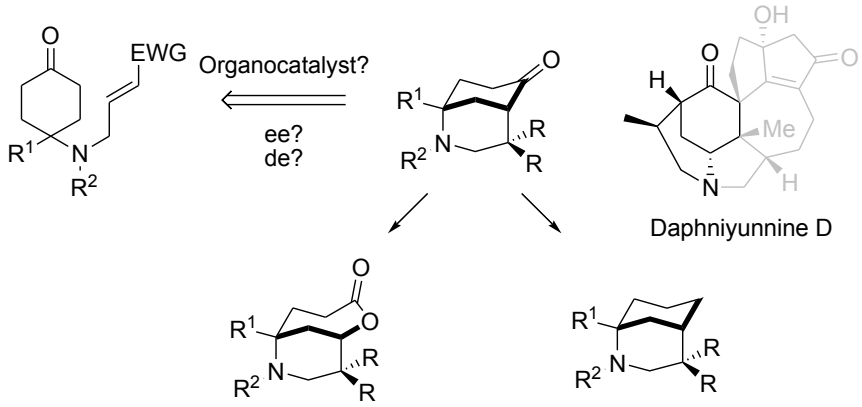
With optimal conditions identified the reaction scope was probed. Changes to the Michael acceptor and the scaffold were assessed to probe the generality of the reaction and the range of enantioenriched product structures accessible.

Table 5: Scope of the Reaction

Starting Material			Yield [%]	Product	ee [%]	Dr [%]
	**1**	R =Me	88		92	97:3
	14	Et	89		90	>98
	15	i-Bu	89		92	>98
	16	t-Bu	86		91	>98
	17	Bn	86		92	>98
	18	Ph	82		92	>98
	**5**		79		81	>98

5mol% Catalyst, 1.25mol% benzoic acid. DCM , 45 ^{o}C; [substrate] = 0.2 M

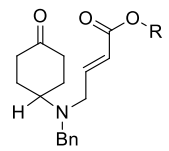
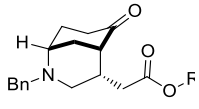
To see further scope of this methodology we synthesized substrates of different scaffold. Products obtained using this methodology will have potential use in the synthesis of key building blocks for members of the daphniphylum families (Scheme 2).



Scheme 2: New Substrate Design

Results are summarized in Table 6. All substrates delivered products with good yields and excellent diastereo and enantioselectivities.

Table 6: Scope of the Reaction

Starting Material			Yield [%]	Product	Ee [%]	Dr [%]
	**19**	R = Et	84		96	>98
	20	Bn	89		97	>98
	21	*c*-Hex	85		96	>98
	22	i-Pr	76		99	>98
	23	Me	90		87	>98

24	Ph	72	97	>98

5mol% Catalyst, 2.5mol% benzoic acid. DCM , 50 ^{o}C; [substrate] = 0.2 M

B.1.5 *Determination of Absolute Stereochemistry:*

Absolute and relative stereochemistry was determined by single crystal X-ray diffraction on **5 (Figure)** and relative stereochemistry was determined for **20** to match**.** In both cases, the same stereochemistry was observed with the electron withdrawing group of the acceptor positioned on the concave face of the [3,3,1] bicyclic scaffold.

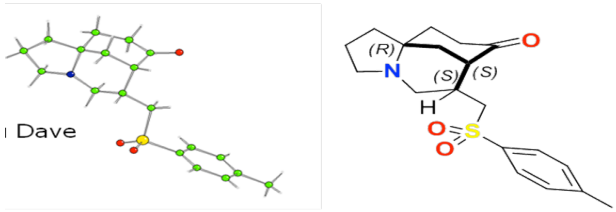


Figure 4: Single Crystal X-Ray Structures

2) SUMMARY OF THE PROGRESS OF THE RESEARCH TRAINING

2-1) Research Skills and techniques:
NMR techniques, GC, HPLC, *etc.*, and the determination of enantiomeric excess using a variety of methods.

2-2) Communication skills:
Results, progress and the work plan for the near future have been discussed on a weekly basis, and the presentation of results to the group have been made every week following the group's usual timetable. Weekly group meetings offered the opportunity for in-depth discussions involving all post-doctoral and post-graduate workers. In addition, weekly one-to-one meetings with Prof. Dixon have been often used to discuss progress, strategy and the direction of the research.