UNIVERSITY GRANTS COMMISSION
BAHADUR SHAH ZAFAR MARG
NEW DELHI – 110 002

Annual Report of the work done on the Major Research Project.

1.	Project report No. 1st/2nd/3rd/Final	Final
2.	UGC Reference No.	F.No.37-192/2009(SR)
3.	Period of report:	01-02-2010 to 31-01-2013
4.	Title of research project:	Organocatalytic approach to Stereoselective Friedel-Crafts alkylation reactions
5. (a)	Name of Principal Investigator	Swapandeep Singh Chimni
(b)	Department and University/ College where work has progressed	Department of Chemistry Guru Nanak Dev University Amritsar 143005
6.	Effective date of starting of the project:	01-02-2010
7.	Grant approved and expenditure incurred during the period of the report:	
(a)	Total amount approved Rs.	Rs.12,53,393/-
(b)	Total amount released Rs.	Rs. 11,77,934 /-
(b)	Total expenditure Rs.	Rs.11,77,934 /-
(c)	Report of the work done:	Annexure 1
(d)	Brief objective of the project:	
	The use of chiral bifunctional organocatalysts especially derived from Cinchona alkaloids for the synthesis of new potentially bioactive chiral enitities via Friedel-Crafts reaction of different arenes to different acceptors.	
(e)	Work done so far and result achieved and publications, if any, resulting from the work (Give details of the papers and names of the journals in which it has been published or accepted for publication)	Annexure I Annexure III Communicated - Under preparation -. Presentation in Conferences -.
(f)	Has the progress been according to original plan of work and towards achieving the objective? If not, state reasons	The progress has been as per original plan.
(g)	Please indicate the difficulties, if any, experienced in implementing	

	the project:	
(h)	If project has not been completed, please indicate the approximate time by which it is likely to be completed. A summary of the work done for the period (annual basis) may please be sent to the Commission on a separate sheet.	N.A.
(i)	If the project has been completed, please enclose a summary of the findings of the study. Two bound copies of the final report of work done may also be sent to the Commission	Annexure II
(j)	Any other information which would help in evaluation of work done on the project. At the completion of the project, the first report should indicate the output, such as (a) Manpower trained (b) Ph.D. awarded (c) Publication of results (d) other impact, if	(a) One student joined the project. (b) He has submitted his Ph.D. thesis in the area of the project. (c) All results have been published. (d) New knowledge has been acquired for organocatalytic transformations.

(Signature of Principal Investigator) (Registrar/Principal)

Annexure 1

Progress Report

The Friedel-Crafts (F-C) reaction, one of the oldest organic synthetic methods, is still one of the most powerful carbon-carbon bond forming reaction from benchtop experiments to industrial processes for procuring valuable building blocks.[1] Although Friedel-Crafts reaction has proven its significance since its discovery in 1877,[2] but the catalytic asymmetric versions of this methodology have been actively developed during the last three decades.[60] The first example of catalytic asymmetric Friedel-Crafts reaction was reported by Bigi *et al.* in 1985, using chiral alkoxyaluminum chloride catalyst for *ortho*-alkylation of phenols.[3] Since then, many groups have directed their efforts for developing new routes to devise highly efficient strategies for asymmetric Friedel-Crafts reaction. The recent upsurge in the development of asymmetric catalytic Friedel-Crafts reaction is based on the development of chiral transition metal based catalysts and organocatalysts for this transformation. While the initial examples of catalytic asymmetric Friedel-Crafts reaction describes a metal-catalyzed addition of aromatic substrates to electron deficient σ-(epoxide opening) and π-systems (1,2-carbonyl and 1,4-conjugate additions), but now-a-days, the field of organocatalysis has led to the development of new asymmetric protocols for enantioselective Friedel-Crafts reactions. Organocatalytic asymmetric Friedel-Crafts reaction provides a highly efficient method for the synthesis of valuable chiral arene derivatives that can serve as precursors for asymmetric synthesis of natural products, bioactive molecules and pharmaceuticals (**Figure 6**) . *Aza*-Friedel-Crafts reaction involves 1,2-addition of aromatic (substituted benzene, phenol, etc.) and hetero-aromatic (indole, pyrrole, furan, etc.) compounds to imine derivatives. The stereoselective version of this reaction is an atom-economical approach for the synthesis of bioactive chiral amine derivatives.[4] The seminal work on the asymmetric *aza*-Friedel-Crafts

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[1] a) G. A. Olah, R. Krishnamurti, G. K. S. Prakash, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming); Pergamon Press, Oxford, **1991**; *vol. 3*, p 293; b) R. M. Roberts, A. A. Khalaf, *Friedel-Crafts Alkylation Chemistry*; Marcel Dekker, New York, **1984**; c) *Friedel-Crafts Chemistry* (Ed.: G. A. Olah), Wiley, New York, **1973**; d) *Friedel-Crafts and Related Reactions* (Ed.: G. A. Olah), Wiley-Interscience, New York, **1963–65**; vols. *1-4*.

[2] a) C. Friedel, J. M. Crafts, *C. R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392; b) C. Friedel, J. M. Crafts, *C. R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1450.

[3] a) F. Bigi, G. Casiraghi, G. Casnati, G. Sartori, G. G. Fava, M. F. Belicchi, *J. Org. Chem.* **1985**, *50*, 5018.

[4] For selected examples on asymmetric aza-Friedel-Crafts reaction, see: a) P. Yu, J. He, C. Guo*, Chem. Commun.* **2008**, 2355; b) G. B. Rowland, E. B. Rowland, Y. Liang, J. A. Perman, J. C. Antilla, *Org. Lett.* **2007**, *9*, 4065; c) M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129,* 292; d) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-

reaction was reported by Johannsen in 1999 using chiral copper complex for the 1,2-addition of indole derivatives to *N*-tosyl-protected α-iminoester, for procuring optically active indole α-amino acid derivatives.[5] In 2004, Terada and co-workers developed the first organocatalytic asymmetric aza-Friedel-Crafts reaction, employing chiral phosphoric acid as catalyst for 1,2-addition of furan derivatives to aldimines.[6] Since then, significant developments have been made in the asymmetric organocatalytic aza-Friedel-Crafts reaction catalyzed by chiral phosphoric acids and chiral thiourea organocatalysts.

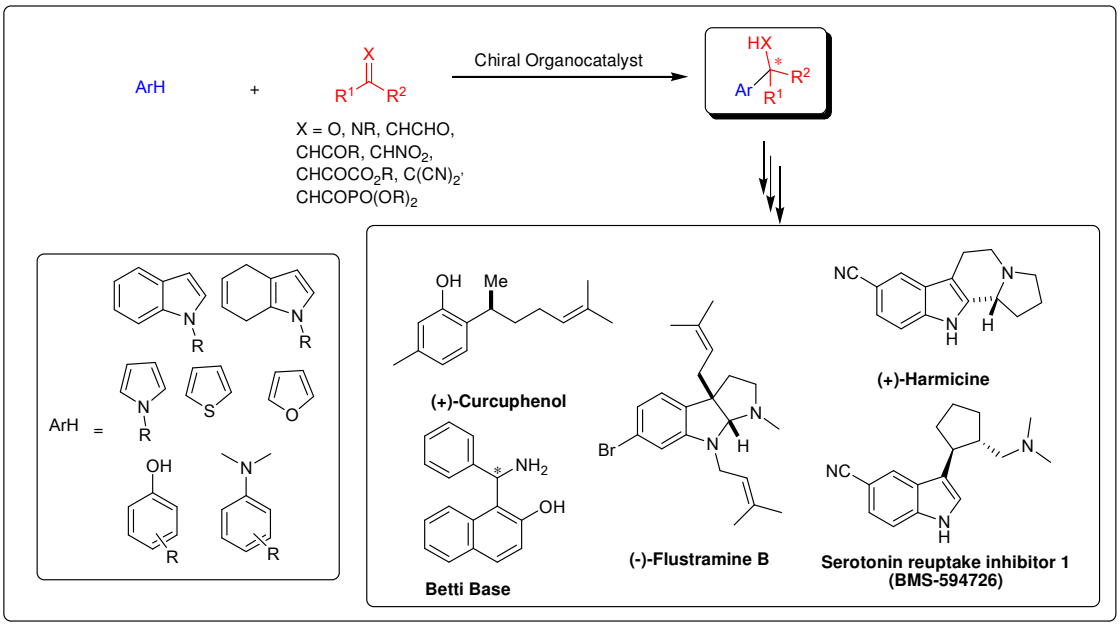

Figure 1 Organocatalytic enantioselective Friedel-Crafts reaction and application of the Friedel-crafts products.

Our work has been divided into mainly four parts

1. Organocatalytic asymmetric friedel crafts reaction of indoles with isatins
2. Organocatalytic asymmetric aza friedel crafts reaction of napthols with imines
3. Asymmetric organocatalytic Michael addition to nitrodienes
4. Friedel-Crafts reaction of indoles with electron deficient olefins with water compatible organocatalyst

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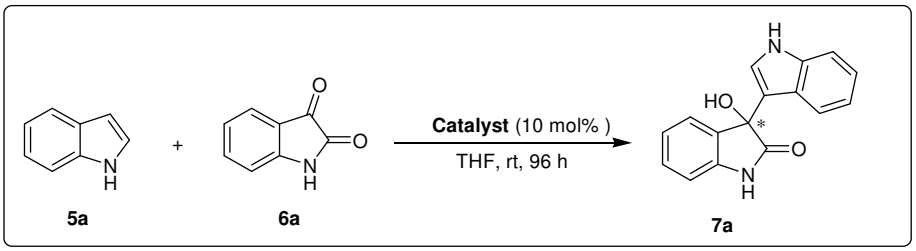
M. Zhang, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2007**, *46*, 5565; e) G.-W. Zhang, L. Wang, J. Nie, J.-A. Ma, *Adv. Synth. Catal.* **2008**, *350*, 1457; f) Q. Kang, X.-J. Zheng, S.-L. You, *Chem. Eur. J.* **2008**, *14*, 3539.

[5] M. Johannsen, *Chem. Commun*. **1999**, 2233.

[6] D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004,** *126,* 11804.

Organocatalytic asymmetric friedel crafts reaction of indoles with isatins: Initially, Friedel-Crafts reaction of indole (5a) with isatin (6a) in the presence of 10 mol% of quinidine (QD) in THF at room temperature was investigated (Scheme 1). The progress of the reaction was monitored on TLC which showed the formation of a new product with R_f: 0.3 in hexane : ethyl acetate (4 : 6). After running the reaction for 96 hours the product was purified on silica gel column chromatography using hexane : ethyl acetate (4 : 6) as eluents. The product was isolated in 62% yield and analyzed by NMR spectroscopy.



Scheme 1 Model reaction for organocatalytic enantioselective Friedel-Crafts reaction indole with isatin catalyzed by *Cinchona*-derived organocatalysts.

Effect of Catalyst: Encouraged by this result, the catalytic potential of other natural *Cinchona* alkaloids quinine (QN), cinchonidine (CD), cinchonine (CN), and other modified *Cinchona* alkaloids cupreine (CPN), cupreidine (CPD), benzylcupreine (BnCPN), benzylcupreidine (BnCPD), by C9-thiourea derivative of cinchonidine (CDT) and quinine (QNT) for enantioselective Friedel-Crafts reaction of indole (5a) with isatin (6a) was evaluated. The results are shown in Table 1.

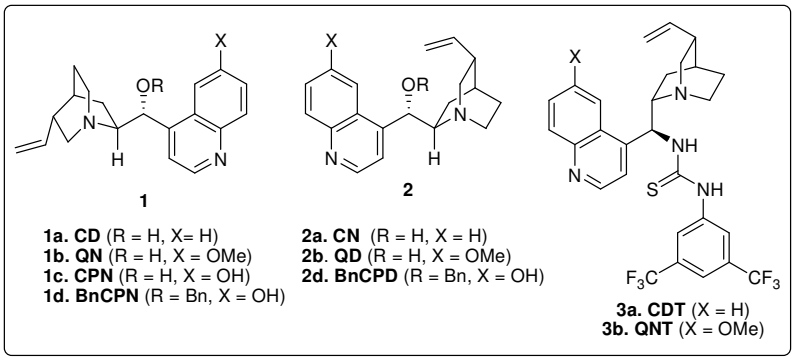


Figure 7 Structure of *Cinchona* derived organocatalysts.

Optimization of reaction condition: In order to increase the yield and enantioselectivity different conditions were applied. With increase in temperature from ambient to higher temperature increases the yield but decreases the enantioselectivity.). However, increasing the catalyst loading leads to increased yield without any significant effect on the

Table 1 Catalyst screening for enantioselective Friedel-Crafts reaction of indole (5a) with isatin (6a).[a]

Entry	Catalysts	Yield [%][b]	*ee* [%][c]
1	**QD**	62	52
2	**QN**	61	-53
3	**CD**	32	-60
4	**CN**	33	58
5	**CPN**	81	82
6	**BnCPN**	83	90
7	**BnCPD**	82	-85
8	**CDT**	31	29
9	**QNT**	29	31

[a] Reaction conditions: 0.250 mmol isatin (**6a**), 0.375 mmol of indole (**5a**) and 10 mol% of catalyst in THF. [b] Yield refers to isolated yield after column chromatography. [c] *ee* refers to *enantiomeric excess*

enantioselectivity (entries 4-5, Table 2). The lower catalyst loading resulted in lower yield (63%) and lower enantioselectivity (85% *ee*). Interestingly, performing the reaction in the presence 10 mol% of **BnCPN** and 4Å molecular sieves (MS) results in the formation of product in 82% yield and increased enantioselectivity of 95% *ee* (entry 7, Table 2). This is probably due to the fact that molecular sieves absorb the traces of moisture in the solvent thus facilitating the hydrogen bonding of catalyst with the substrates.

Table 2 Optimization of reaction condition for enantioselective Friedel-Crafts reaction of indole (5a) with isatin (6a).[a]

Entry	BnCPN[x mol %]	Temperature[°C]	Additive	Yield[%][b]	*ee*[%][c]
1	10	27	-	83	90
2	10	50	-	97	80
3	10	40	-	94	85
4	15	27	-	93	91
5	20	27	-	95	90
6	5	27	-	63	85
7	10	27	4Å MS	82	95
8	15	27	4Å MS	92	96

[a] Reaction conditions: 0.250 mmol isatin (**6a**), 0.375 mmol of indole (**5a**) and x mol% of **BnCPN** in THF. [b] Yield refers to isolated yield after column chromatography. [c] *ee* refers to *enantiomeric excess* determined by chiral HPLC.

Effect of solvent: Screening of different organic solvents with 15 mol% **BnCPN** and 4Å MS as additive shows that the use of THF as solvent provides best enantioselectivity of **7a** (entry 1, Table 3). In chlorinated solvents such as dichloromethane, chloroform and 1,2-dichloroethane, **7a** was isolated in high yield (99%, 96% and 94%, respectively), but

enantioselectivity was rather low (80% *ee*, 60% *ee* and 49% *ee*) (entries 6-8, Table 3). In polar protic solvents like ethanol and methanol, **7a** was isolated in 94% and 95% yield; and 49% *ee* and 33% *ee*, respectively (entries 9-10, Table 3). Other solvents such as ethyl acetate (entry 11, Table 3) and DMF (entry 12, Table 3) proved to be less efficient in term of product yield and enantio-induction. So the best optimized reaction condition for **BnCPN** catalyzed enantioselective Friedel-Crafts reaction of indole and isatin constitutes, the use of 15 mol% of **BnCPN** organocatalyst, THF as the solvent and 4Å MS as additive at room temperature. In this reaction condition the product **7a** was isolated in 92% yield and 96% *ee*.

Table 3 Solvent screening for BnCPN catalyzed Friedel-Crafts reaction of indole (5a) with isatin (6a).[a]

Entry	Solvents	Yield [%][b]	*ee* [%][c]
1	THF	92	96
2	Diethyl ether	38	80
3	MTBE	33	71
4	1,4-Dioxane	83	82
5	Toluene	41	39
6	CH_2Cl_2	99	80
7	$CHCl_3$	96	60
8	$ClCH_2CH_2Cl$	94	49
9	EtOH	94	49
10	MeOH	95	33
11	EtOAc	50	18
12	DMF	15	46
13[d]	THF	93	-89

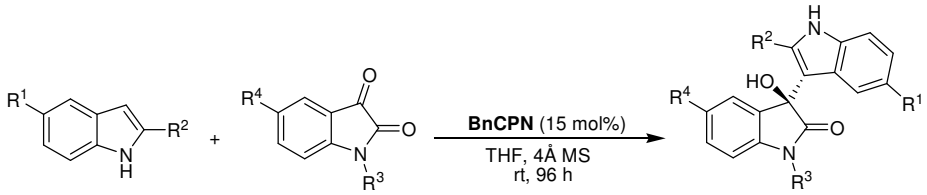
[a] Reaction conditions: 0.250 mmol isatin (**6a**), 0.375 mmol of indole (**5a**), 100 mg of 4Å molecular sieves and 15 mol% of **BnCPN** in dry THF. [b] Yield refers to isolated yield after column chromatography. [c] *ee* refers to *enantiomeric excess* determined by chiral HPLC. [d] **BnCPD** was used as catalyst.

Substrate scope: Once armed with the optimized reaction condition, the substrate scope was investigated by screening different indole and isatin derivatives. 5-Flouro, 5-chloro and 5-bromoisatins (**6b**, **6c** and **6d**) react well with indole (**5a**) yielding the corresponding 3-substituted-3-hydroxyindoles (**7b**, **7c** and **7d**) in 97%, 98% and 99% yield; and 83% *ee*, 90% *ee* and 92% *ee*, respectively (entries 2-4, Table 4). The reaction of 5-nitroisatin (**6e**) with **5a** occurs with high yield of 98% and good enantioselectivity of 83% *ee* (entry 5, Table 4). The *N*-alkylated isatins (**6f**, **6g** and **6h**) also reacted with indole (**5a**) to provide corresponding

adducts (**7f**, **7g** and **7h**) in 89%, 88% and 99% yield; and 85% *ee*, 88% *ee* and 88% *ee*, respectively (entries 6-8, Table 4).

The 5-substituted indoles also reacted efficiently with isatin derivatives in the presence of **BnCPN**. The reactions of 5-methoxyindole (**5b**) with isatin derivatives (**6a**, **6d** and **6g**) provide corresponding oxindole derivatives (**7i**, **7j** and **7k**) in 97%, 99% and 95% yield; and 97% *ee*, 99% *ee* and 93% *ee*, respectively (entry 9-11, Table 4). 5-Bromoindole (**5c**) and 5-nitroindole (**5d**) reacts with isatin (**6a**) providing **7l** and **7m** in 92% and 90% yield; and 80% *ee* and 79% *ee*, respectively (entries 12-13, Table 4). 2-Methylindole (**5e**) reacts with isatin (**6a**) to provide **7n** in 96% yield and only in 17% *ee* (entry 14, Table 4). Enantiomeric excess of the Friedel-Crafts adducts could be enriched to >99% after crystallization from *iso*-propanol (entries, 1 and 9, Table 4).

Table 4 Substrate scope for BnCPN catalyzed Friedel-Crafts reaction of indole derivatives (5) with isatin derivatives (6).[a]



5 6 7

Entry	5 (R^1, R^2)	6(R^3, R^4)	7	Yield[%][b]	*ee*[%][c]
1	**5a** (R^1 = H, R^2 = H)	**6a** (R^3 = H, R^4 = H)	**7a**	92	96 (>99)[d]
2	**5a** (R^1 = H, R^2 = H)	**6b** (R^3 = H, R^4 = F)	**7b**	97	83
3	**5a** (R^1 = H, R^2 = H)	**6c** (R^3 = H, R^4 = Cl)	**7c**	98	90
4	**5a** (R^1 = H, R^2 = H)	**6d** (R^3 = H, R^4 = Br)	**7d**	99	92
5	**5a** (R^1 = H, R^2 = H)	**6e** (R^3 = H, R^4 = NO_2)	**7e**	98	83
6	**5a** (R^1 = H, R^2 = H)	**6f** (R^3 = Me, R^4 = H)	**7f**	89	85
7	**5a** (R^1 = H, R^2 = H)	**6g** (R^3 = Bn, R^4 = H)	**7g**	88	88
8	**5a** (R^1 = H, R^2 = H)	**6h** (R^3 = Me, R^4 = Br)	**7h**	99	88
9	**5b** (R^1 = MeO, R^2 = H)	**6a** (R^3 = H, R^4 = H)	**7i**	97	97 (>99)[d]
10	**5b** (R^1 = MeO, R^2 = H)	**6d** (R^3 = H, R^4 = Br)	**7j**	99	99
11	**5b** (R^1 = MeO, R^2 = H)	**6g** (R^3 = Bn, R^4 = H)	**7k**	95	93
12	**5c** (R^1 = Br, R^2 = H)	**6a** (R^3 = H, R^4 = H)	**7l**	92	80
13	**5d** (R^1 = NO_2, R^2 = H)	**6a** (R^3 = H, R^4 = H)	**7m**	90	79
14	**5e** (R^1 = H, R^2 = Me)	**6a** (R^3 = H, R^4 = H)	**7n**	96	17

[a] Reaction conditions: 0.250 mmol isatins **(6)**, 0.375 mmol of indoles **(5)**, 15 mol% of **BnCPN** and 100 mg of 4Å molecular sieves in dry THF at rt. [b] Yield refers to isolated yield after column chromatography. [c] *ee* refers to *enantiomeric excess* determined by chiral HPLC. [d] *ee* value after crystallization from *iso*-propanol.

The absolute configuration of stereogenic center in the adduct (**7**) has been assigned as (*S*) on the basis of the X-ray structure of **7a** (**Figure 3**).[7] The single crystal X-ray structure of **7a** indicates that the crystal has an orthorhombic crystalline state with symmetrical space group P 21 21 21.

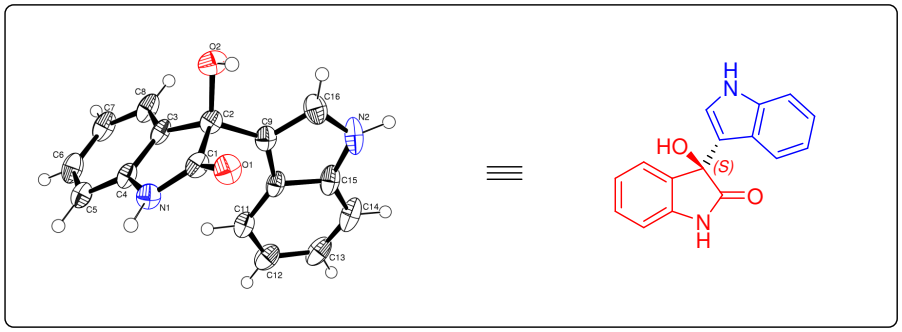


Figure 3 X-ray structure of **6a**.

Transition state involving a ternary complex between the catalyst, isatin and indole has been proposed (**Figure 4**). In the transition state the 6'-OH of the catalyst activate isatin with hydrogen bonding and the tertiary nitrogen of the catalyst activate and orient indole for the *si*-face attack to provide (*S*) enantiomer of Friedel-Crafts product (**7**).

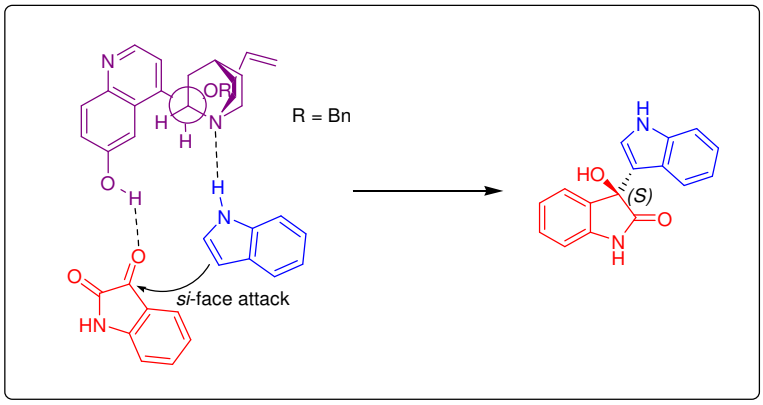
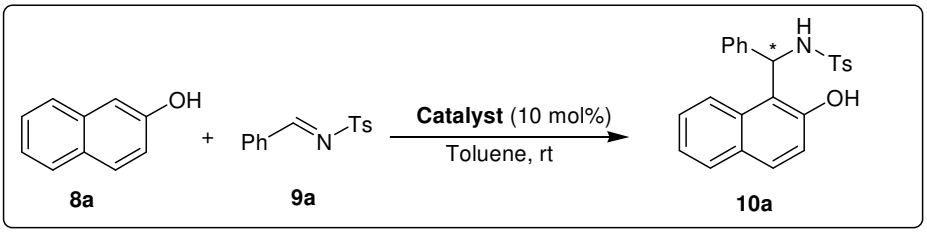


Figure 4 Plausible transition state for the enantioselective synthesis of 3-indolyl-3-hydroxyoxindole.

[7] CCDC 874066 contains the supplementary crystallographic data of **7a**.

Organocatalytic asymmetric *aza* Friedel-Crafts reaction of napthols with imines

Due to the successful application of 6'-OH *Cinchona* alkaloid (cupreine and cupreidine derivative) in Friedel-Crafts reaction of indole with isatin , So, it was planned to investigate the application of 6'-OH *Cinchona* alkaloids for enantioselective aza-Friedel-Crafts reaction of naphthols with imines. The aza-Friedel-Crafts reaction between 2-naphthol (**8a**) and *N*-tosylimine (**9a**) was investigated by using 10 mol% of cupreine (**CPN**) as catalyst in toluene as solvent (**Scheme 2**). The crude product was purified by silica gel column chromatography using hexane : ethyl acetate (7 : 3) as eluents. The pure product was isolated in 92% yield and was characterized as 1-[phenyl(tosylamino)methyl]naphthalen-2-ol (**10a**) on the basis of ^{1}H NMR, ^{13}C NMR and mass spectroscopic analysis.



Scheme 2 Model reaction for organocatalytic enantioselective aza-Friedel-Crafts reaction catalyzed by *Cinchona*-derived organocatalysts.

Effect of catalyst: In order to discover the best organocatalyst for this transformation other 6'-OH *Cinchona* alkaloids were screened for the aza-Friedel-Crafts reaction of 2-naphthol (**8a**) with *N*-tosylimine (**9a**) to procure optically active aminonaphthol (**10a**) with highest enantioselectivity. The aza-Friedel-Crafts reaction of **8a** with **9a** catalyzed by natural *Cinchona* alkaloids and 6'-OH *Cinchona* alkaloid derivatives affords **10a** in low to moderate enantioselectivity. In order to search for an organocatalyst that catalyzes the aza-Friedel-Crafts reaction in highly enantioselective manner, So, it was planned to synthesize the *Cinchona*-derived bifunctional organocatalysts with an ester group at C9 of cupreine and cupreidine. Such organocatalyst may provide the right type of orientation for the reactants in the transition state so as to obtain the product with high enantioselectivity. So, benzoyl, naphthoyl, pivaloyl and acetyl derivatives of cupreine were synthesized and used for catalyzing the model reaction.

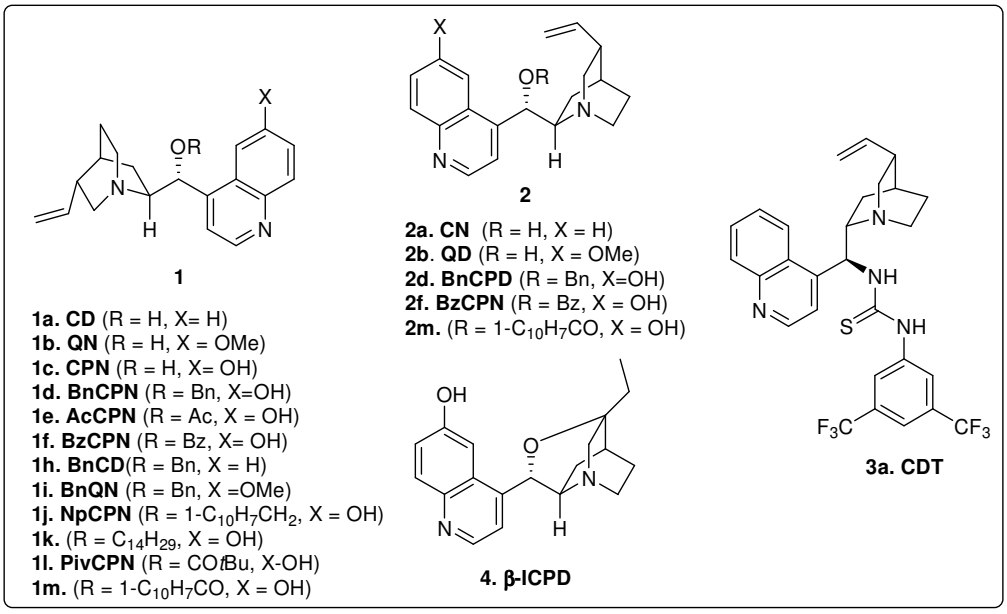


Figure 5 Structure of *Cinchona* derived organocatalysts.

Table 5 Catalyst screening for aza-Friedel-Crafts reaction of 2-naphthol (**8a**) with *N*-tosylimine (**9a**).[a]

Entry	Catalyst	Time[h]	Yield[%][b]	*ee*[%][c]
1	**CPN**	4	92	39
2	**BnCPN**	5	94	46
3	**BnCPD**	5	93	-40
4	**NpCPN**	5	93	49
5	**1k**	5	89	45
6	**β-ICPD**	6	91	-42
7	**CD**	5	92	-5
8	**QN**	6	91	-5
9	**CN**	5	94	6
10	**QD**	5	91	6
11	**BnCD**	24	78	9
12	**BnQN**	24	81	6
13	**CDT**	5	85	7
14	**BzCPN**	10	90	78
15	**1m**	10	89	77
16	**AcCPN**	10	87	76
17	**PivCPN**	12	85	75
18	**BzCPD**	10	89	-75
19	**2m**	12	87	-75

[a] Reaction conditions: 1.875 mmol 2-naphthol (8a), 0.125 mmol of imine (9a) and 10 mol% of catalyst in toluene at rt. [b] Yield refers to isolated yield after column chromatography. [c] *ee* refers to *enantiomeric excess* determined by HPLC analysis.

Optimization of reaction condition: In order to increase the yield and enantioselectivity different conditions were applied. The effect of additives was evaluated on **BzCPN** catalyzed aza-Friedel-Crafts reaction of **8a** with **9a**. The use of 4Å molecular sieves (MS) as additive resulted in slight improvement in the enantioselectivity (80% *ee*) of **10a** (entry 1, Table 6), whereas the use of benzoic acid as an additive resulted in a lower reaction rate and a slightly lower enantioselectivity (73% *ee*) (entry 2, Table 6). So, for all further optimization 4Å molecular sieves were used as additive. Performing the reaction at –5 °C resulted in prolonged reaction time without any improvement in the enantioselectivity of the product (entry 3, Table 6). Lowering the catalyst loading to 5 mol% provides adduct (**10a**) in high yield (88%), without any loss in enantioselectivity (up to 84% *ee*) (entries 4-5, Table 6). Further lowering of the catalyst loading to 2.5 mol% resulted in a lower yield (62%) and good enantioselectivity of 78% *ee* (entry 6, Table 6).

Table 6 Optimization of reaction condition for *aza*-Friedel-Crafts reaction of 2-naphthol (**8a**) with *N*-tosylimine (**9a**).[a]

Entry	Catalyst [x mol%]	Additive	Time [h]	Yield [%][b]	*ee* [%][c]
1	**BzCPN** (10)	4Å MS	10	89	80
2	**BzCPN** (10)	$PhCO_2H$	15	83	73
3[d]	**BzCPN** (10)	4Å MS	32	89	79
4	**BzCPN** (5)	-	24	88	78
5	**BzCPN** (5)	4Å MS	24	88	84
6	**BzCPN** (2.5)	4Å MS	24	62	78
7	**BzCPD** (5)	4Å MS	24	85	-76

[a] Reaction conditions: 1.875 mmol 2-naphthol (8a), 0.125 mmol of imine (9a) and x mol% of catalyst in toluene at rt. [b] Yield refers to isolated yield after column chromatography. [c] *ee* refers to *enantiomeric excess* determined by HPLC analysis. [d] Reaction was performed at -5 ºC.

Effect of solvent: In order to identify the best solvent for this transformation, different solvents were screened with 5 mol% of **BzCPN** as catalyst and 4Å molecular sieves as additive (Table 7). On performing the reaction in xylene, **10a** was obtained in 86% yield and 62% *ee* (entry 1, Table 7). The chlorinated solvents such as dichloromethane, 1,2-dichloroethane and chloroform provided **10a** in 75%, 73% and 84% yield; and 72% *ee*, 63% *ee* and 71% *ee*, respectively (entries 2-4, Table 7). In THF, the product **10a** was isolated in 25% yield and 79% *ee* (Entry 5, Table 7). In diethyl ether, poor yield (18%) and low enantio-

differentiation (43% *ee*) was observed (entry 6, Table 7). Thus, toluene was selected as best solvent for **BzCPN** catalyzed aza-Friedel-Crafts reaction (entry 7, Table 7).

Table 7. Solvent screening for BzCPN catalyzed aza-Friedel-Crafts reaction of 2-naphthol (8a) with *N*-tosylimine (9a).[a]

Entry	Solvent	Yield[%][b]	ee[%][c]
1	Xylene	86	62
2	CH_2Cl_2	75	72
3	$ClCH_2CH_2Cl$	73	63
4	$CHCl_3$	84	71
5	THF	25	79
6	Diethyl ether	18	43
7	Toluene	88	84

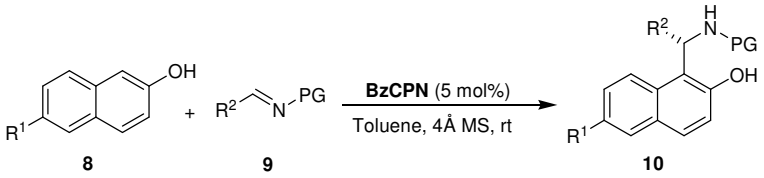
[a] Reaction conditions: 1.875 mmol 2-naphthol (8a), 0.125 mmol of imine (9a), 5 mol% of BzCPN, 20 mg of 4Å molecular sieves (MS) in toluene at rt for 24 hours. [b] Yield refers to isolated yield after column chromatography. [c] *ee* refers *enantiomeric excess* determined by HPLC analysis

Substrate scope: The best optimized reaction conditions for the aza-Friedel–Crafts reaction of 2-naphthol with *N*-tosylimine providing aza-Friedel-Crafts adduct (10a) in 88% yield and 82% *ee*, consists of 5 mol% of BzCPN as catalyst, 4Å MS as additive and toluene as the solvent at room temperature. Further, the scope of this method was examined by reacting different *N*-sulfonylimine derivatives (9a–9j) with 2-naphthol (8a) using 5 mol% of BzCPN as catalyst and 4Å MS as additive in toluene at room temperature (Table 8). The *N*-tosylimine substituted with either an electron-withdrawing or an electron-donating group on the phenyl ring gave respective *aza*-Friedel–Crafts products in high yield and high enantioselectivity. The imines substituted with electron withdrawing *ortho*- and *para*- substituents such as fluoro and chloro, on the phenyl ring provide the respective products (10b, 10c, 10d and 10e) in excellent yield of 99%, 98%, 97% and 99%; and very good enantioselectivity of 92% *ee*, 93% *ee*, 84% *ee* and 87% *ee*, respectively. (entries 2-5, Table 8).

After the successful exploration of the catalytic potential of **BzCPN** for enantioselective *aza*-Friedel-Crafts reaction of naphthol derivatives, sesamol was used as a donor for *aza*-Friedel-Crafts with imines. Sesamol is a representative structural motif often observed in natural alkaloids and biologically active compounds.[8] The reaction of sesamol (**11**) with *N*-tosylimines (**9b** and **9d**) catalyzed by **BzCPN (**10 mol%) provide aza-Friedel-Crafts adducts (**12a** and **12b**) in 91% and 85% yield; and 89% *ee* and 76% *ee*, respectively (**Scheme 3**).

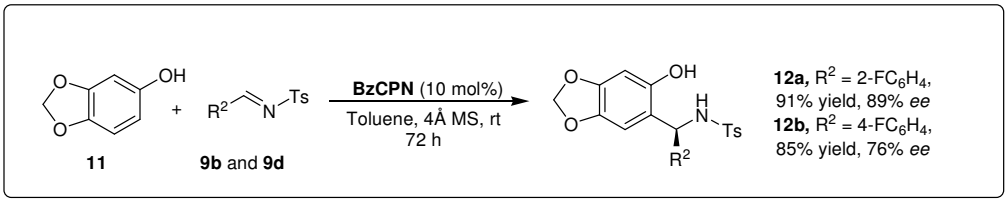
Table 8 Substrate scope for BzCPN catalyzed asymmetric aza-Friedel-Crafts reaction of 2-naphthols (22) with *N*-sulfonylimines (23).[a]

[8] a) X. Chen, J. P. Zhu, *Angew. Chem. Int. Ed.* **2007**, *46*, 3962; b) C. Rondot, J. Zhu, *Org. Lett.* **2005**, *7*, 1641; c) F. Bailly, C. Queffelec, G. Mbemba, J.-F. Mouscadet, P. Cotelle, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5053; d) E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, A. Haidour, J. M. Ramos, R. A. Manzaneda, R. Tapia, H. Es-Samti, A. Fernández, I. Barranco, *Eur. J. Org. Chem.* **2009**,1139.



Entry	8 (R^1)	9 (R^2, PG)	10	Yield [%][b]	*ee* [%][c]
1	**8a** (R^1 = H)	**9a** (R^2 = Ph, PG = Ts)	**10a**	88	84
2	**8a** (R^1 = H)	**9b** (R^2 =2-FC_6H_4, PG = Ts)	**10b**	99	92
3	**8a** (R^1 = H)	**9c** (R^2 = 2-ClC_6H_4, PG =Ts)	**10c**	98	93
4	**8a** (R^1 = H)	**9d** (R^2 = 4-FC_6H_4, PG = Ts)	**10d**	97	84
5	**8a** (R^1 = H)	**9e** (R^2 = 4-ClC_6H_4, PG = Ts)	**10e**	98	87
6	**8a** (R^1 = H)	**9f** (R^2 = 3-$NO_2C_6H_4$, PG = Ts)	**10f**	97	60
7	**8a** (R^1 = H)	**9g** (R^2 = 4-Me C_6H_4, PG = Ts)	**10g**	87	84
8	**8a** (R^1 = H)	**9h** (R^2 = 4-$MeOC_6H_4$, PG = Ts)	**10h**	82	81
9	**8a** (R^1 = H)	**9i** (R^2 = 2-furanyl, PG = Ts)	**10i**	95	82
10[d]	**8a** (R^1 = H)	**9j** (R^2 = Ph, PG = SO_2Ph)	**10j**	71	48
11[d]	**8b** (R^1 = MeO)	**9a** (R^2 = Ph, PG = Ts)	**10k**	89	86
12	**8b** (R^1 = MeO)	**9b** (R^2 = 2-FC_6H_4, PG = Ts)	**10l**	94	99
13[d]	**8c** (R^1 = Br)	**9a** (R^2 = Ph, PG = Ts)	**10m**	78	74
14	**8c** (R^1 = Br)	**9b** (R^2 = 2-FC_6H_4, PG = Ts)	**10n**	95	79
15[d]	**8d** (R^1 = Bz)	**9a** (R^2 = Ph, PG = Ts)	**10o**	58	72
16[d]	**8d** (R^1 = Bz)	**9b** (R^2 = 2-FC_6H_4, PG = Ts)	**10p**	76	80

[a] Reaction conditions: 1.875 mmol 2-naphthols (**8**), 0.125 mmol of imines (**9**), 5 mol% of **BzCPN**, 20 mg of 4Å molecular sieves at rt for 24 hours. [b] Yield refers to isolated yield after column chromatography. [c] *ee* refers to *enantiomeric excess* determined by HPLC analysis. [d] Reaction carried out for 48 hours.



Scheme 3 **BzCPN** catalyzed enantioselective aza-Friedel-Crafts reaction of sesamol with *N*-tosylimines.

The absolute configuration of 1-[phenyl(tosylamino)methyl]naphthalen-2-ol (**10a**) was assigned as (*S*) on the basis of the single crystal X-ray structure analysis (**Figure 6**).[9]

[9] CCDC-791197 contains the supplementary crystallographic data of **10a** .

The single crystal X-ray structure of **10a** indicates that the crystal has monoclinic crystalline state with symmetrical space group P 21 21 21.

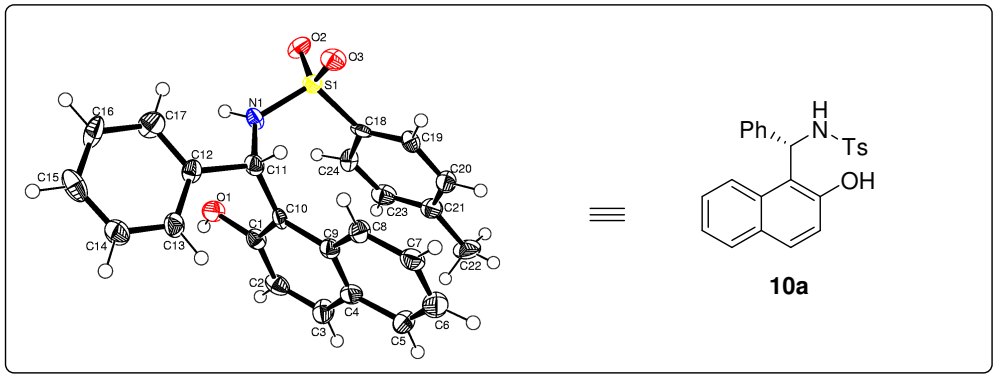


Figure 6 X-ray structure of **10a**.

On the basis of these experimental observations and observed stereochemistry, a transition state involving a ternary complex between the catalyst and the substrates has been proposed. The quinuclidine tertiary amine of the catalyst forms a hydrogen bond with OH group naphthol, thus activating it for nucleophilic attack from C1 on the *re*-face of the imine, which is activated through hydrogen bonding with the 6'-OH group of the catalyst, leading to the formation of (*S*) enantiomer of the product (**Figure 7**).

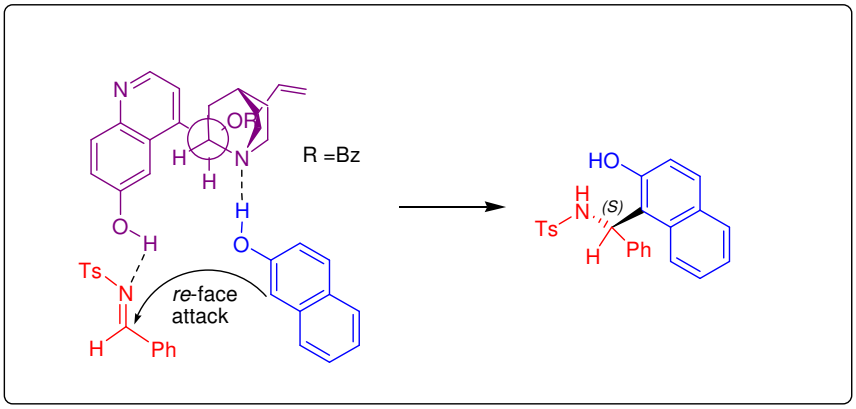


Figure 7 Proposed transition state for **BzCPN** catalyzed asymmetric aza-Friedel-Crafts reaction of 2-naphthol with *N*-sulfonylimine.

Asymmetric organocatalytic Michael addition to nitrodienes

Michael reaction has emerged as one of the most important carbon-carbon bond formation reaction in organic synthesis. In Michael reaction various anionic carbon

species derived from nitroalkanes, malonates or ketoesters, etc., are reacted with a diverse set of acceptor such as α,β-unsaturated carbonyl compounds or nitroalkenes, etc.[10] The asymmetric version of Michael reaction provide wide range of precursors for bioactive molecules and natural products. Although, tremendous success has been achieved in asymmetric Michael reaction employing transition metal catalysts and organocatalysts, but there exists a wide scope in developement of asymmetric Michael reaction employing new substrates and new chiral catalysts. Among various Michael acceptors, nitroalkenes are considered as excellent electrophiles for catalytic asymmetric Michael reaction, due to their high reactivity and hydrogen bond accepting ability of the nitro functionality. The corresponding nitroalkanes are synthetically useful molecules, since the nitro group can be transformed into other valuable functional groups such as amino, oxime, carbonyl and carboxylic acid.[11] The synthetic utility of nitroolefins could be enhanced by the introduction of additional reactive site in addition to nitro-olefinic double bond. Nitrodienes have an additional reactive site *i.e.* a double bond, that can be exploited wisely for the construction of synthetically valuable and potentially bioactive targets. Further, in nitrodienes there exists an additional possibilty of δ-attack rather than β-attack due to the two conjugate double bonds. This feature presents a challenge of regioselective nucleophilic addition at one of the preferred site.

During the exploration of the catalytic potential of bifunctional *Cinchona*-derived organocatalysts for new carbon-carbon bond formation reactions, it was envisaged that high stereo-induction could be achieved in the Michael addition reaction of tri-substituted β-ketoesters with nitrodienes. In order to justify this hypothesis, initially the Michael addition of β-ketoester (**13a**) to nitrodiene (**14a**) catalyzed by 10 mol% of 9-*O*-benzylcupreine (**BnCPN**) in toluene at room temperature was investigated (entry 1, Table 9). The progress of the reaction was monitiored with TLC and reaction was complete in 5 hours. The desired product (**15a**) was isolated in 99% yield, and analyzed with NMR and mass spectroscopic analysis.

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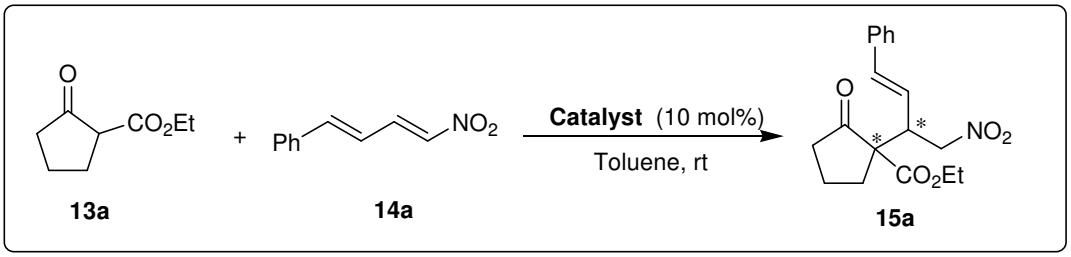
[10] a) R. Little, M. Masjedizadeh, O. Wallquist, J. I. Mcloughlin, *Org. React.* **1995**, *47*, 315; b) B. Mather, K. Viswanathan, K. Miller, T. Long, *Progress in Polymer Science* **2006**, *31*, 487.

[11] a) N. Ono, *The Nitro Group in Organic Synthesis* Wiley-VCH, New York, **2001**; b) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017.



Scheme 4 Model reaction for organocatalytic stereoselective Michael reaction catalyzed by *Cinchona*-derived organocatalysts.

Effect of catalyst: Further, natural *Cinchona* alkaloids *viz.* quinine (**QN**), cinchonidine (**CD)**, cinchonine (**CN**) and quinidine (**QD**) were screened for the conjugate addition of **13a** to **14a**, which provide **15a** in very high yield (98-99%), good diastereoselectivity (90:10 *dr*) and moderate enantioselectivity (40-61% *ee*) (entries 2-5, Table 9). Since **BnCPN** provide **15a** in maximum yield of 99% and highest stereoselectivity of 91:9 *dr* and 97 % *ee* (entry1, Table 9), the further optimizations have been carried out with **BnCPN** as catalyst.

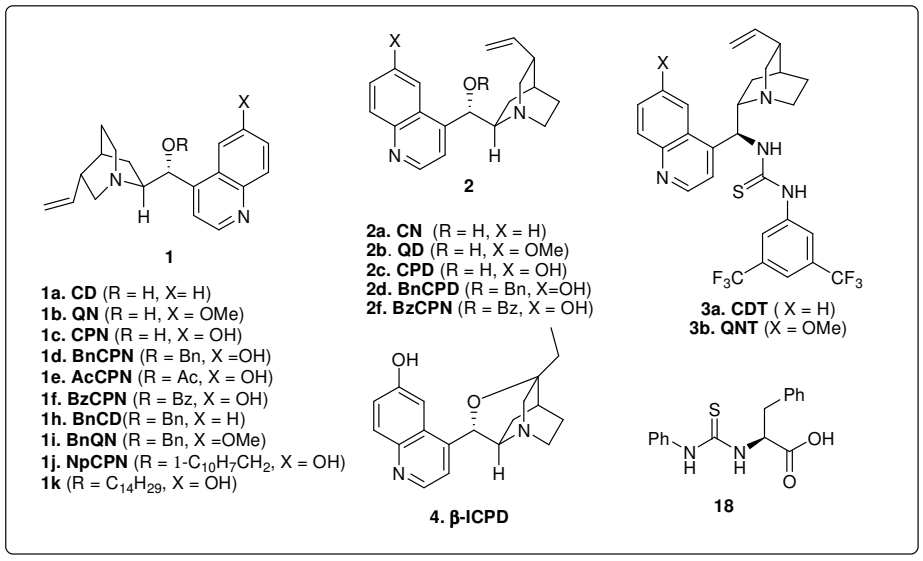


Figure 8 Structure of organocatalysts and additive used.

Table 9 Catalyst screening for Michael reaction of β-ketoester (**13a**) with nitrodiene (**14a**).[a]

Entry	Catalyst	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**BnCPN**	5	99	91:9	97
2	**QN**	6	98	90:10	-61

3	**CD**	6	99	90:10	-45
4	**CN**	6	98	90:10	60
5	**QD**	6	99	90:10	40
6	**BnQN**	10	96	91:9	46
7	**BnCD**	10	97	91:9	44
8	**CPN**	5	99	91:9	91
9	**NpCPN**	5	99	91:9	95
10	**1k**	5	98	91:9	97
11	**BzCPN**	5	97	82:18	97
12	**AcCPN**	5	97	83:17	96
13	**CPD**	5	98	91:9	-89
14	**BnCPD**	5	99	91:9	-94
15	**β-ICPD**	5	98	91:9	-82
16	**CDT**	5	98	95:5	70
17	**QNT**	5	99	95:5	81

[a] Reaction conditions: 0.3 mmol of **13a** and 0.2 mmol of **14a** in 0.2 mL of toluene with 10 mol% of catalyst at rt. [b] Yield refers to isolated yield after column chromatography. [c] *dr* refers to *diastereomeric ratio* determined by HPLC after short column chromatography. [d] *ee* refers to *enantiomeric excess* of major diastereomer.

Optimization of reaction condition: Further, effect of additives such as molecular sieves, benzoic acid and thiouredo acid (18) on the stereoselectivity of BnCPN catalyzed Michael reaction of 13a with 14a was evaluated. All these additives slow down the reaction and did not show any improvement in the enantioselectivity and diastereoselectivity of 15a (entries 1-3, Table 10). The lowering of the catalyst loading from 10 mol% to 1 mol% provides 15a with similar level of stereoselectivity (entries 3-6, Table 10). With 1 mol% of BnCPN the adduct (15a) was isolated in 97% yield, 97% ee and 91:9 dr in 15 hours (entry 6, Table 10). Further lowering of catalyst loading to 0.5 mol%, 0.25 mol% and 0.1 mol% have no effect on the stereochemical outcome of the reaction, but results in lower yield (entries 7-9, Table 10). Thus the catalyst loading of 1 mol% was chosen for further optimization, since it gave optimum yield and stereoselectivity.

Table 10. Optimization of reaction condition for Michael reaction of β-ketoester (**13a**) with nitrodiene (**14a**).[a]

Entry	**BnCPN [x mol%]**	**Additive**	**Time [h]**	**Yield [%][b]**	***dr*[c]**	***ee* [%][d]**
1	10	4Å MS	6	97	91:9	96
2	10	$PhCO_2H$	10	96	91:9	96
3	10	**16**	10	97	91:9	97
4	5	-	6	98	91:9	96
5	2	-	10	99	91:9	97
6	1	-	15	97	91:9	97
7	0.5	-	24	97	91:9	97
8	0.25	-	81	72	91:9	97
9	0.1	-	120	38	91:9	97

[a] Reaction conditions: 0.3 mmol of **13a** and 0.2 mmol of **14a** in 0.2 mL of toluene with x mol% of catalyst at rt. [b] Yield refers to isolated yield after column chromatography. [c] *dr* refers to *diastereomeric ratio* determined after short column chromatography. [d] *ee* refers to *enantiomeric excess* of major diastereomer.

Effect of solvent: A very little effect on the yield and stereoselectivity of Michael adduct (**15a**) was observed by screening different solvents with 1 mol% of **BnCPN** (Table 11). Dichloromethane turns out to be the solvent of choice that provides the product (**15a**) in quantitative yield, 97% *ee* and 94:6 *dr* after 15 hours (entry 4, Table 11).

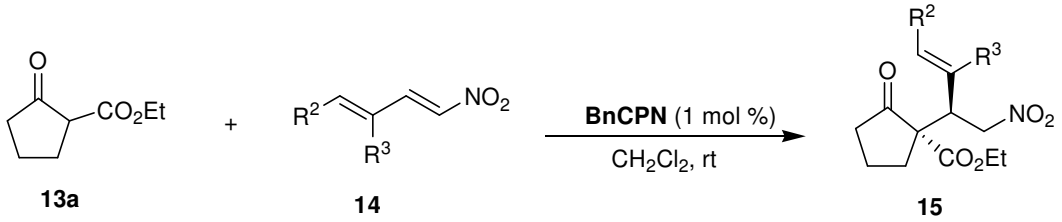
Table 11 Screening of solvents for Michael reaction of β-ketoester (**13a**) with nitrodiene (**14a**).[a]

Entry	Solvent	Time [h]	Yield [%][b]	*dr*[e]	*ee* [%][d]
1	Toluene	15	98	91:9	97
2	Xylene	15	99	91.9	97
3	$CHCl_3$	15	98	90:10	96
4	CH_2Cl_2	15	>99	94:6	97
5	$ClCH_2CH_2Cl$	18	97	94:6	96
6	THF	18	99	93.7	96
7	MTBE	16	98	93:7	97
8	Diethyl ether	12	99	92:8	90
9	DMF	36	26	91.9	84
10	MeOH	36	66	89:11	66
11[e]	CH_2Cl_2	15	99	94:6	-97

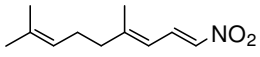
[a] Reaction conditions: 0.3 mmol of **13a** and 0.2 mmol of **14a** in 0.2 mL of solvent with 1 mol% of **BnCPN** at rt. [b] Yield refers to isolated yield after column chromatography. [c] *dr* refers to *diastereomeric ratio* determined after short column chromatography. [d] *ee* refers to *enantiomeric excess* of major diastereomer. [e] Reaction was performed with 1 mol% of **BnCPD**.

Effect of substrate: After optimization, the substrate scope was evaluated by screening different nitrodienes (**14b-14h**) with β-ketoester (**13a**) using **BnCPN** as catalyst in dichloromethane at room temperature (Table 12). **BnCPN** (1 mol%) catalyzes Michael addition of β-ketoester (**13a)** to nitrodienes (**14b** and **14c**) bearing electron withdrawing group on the aromatic ring in 8 hours to provide the desired products (**15b** and **15c**), in 98% and 99% yield; 96:4 *dr* and 93:7 *dr*; and 96% *ee* and 95% *ee*, respectively (entries 2 and 4, Table 12). The nitrodienes (**14d**, **14e** and **14f**) substituted with electron releasing group also reacted with **13a** in the presence of 1 mol% of **BnCPN** to provide 1,4-adducts **15d**, **15e** and **15f** in 92%, 91% and 97% yield; 90:10 *dr*, 89:11 *dr* and 93:7 *dr*; and 91% *ee*, 93% *ee* and 97% *ee*, respectively (entries 6-8, Table 12).

Table 12 BnCPN catalyzed asymmetric Michael reaction of β-ketoester (**13a**) with nitrodienes (**14**).[a]



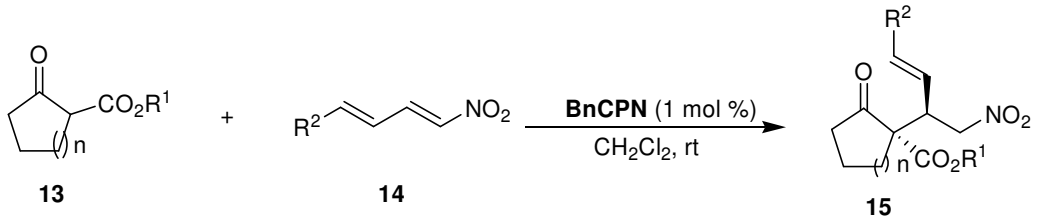
13a **14** **15**

Entry	14 (R^2, R^3)	Time [h]	15	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**14a** (R^2 = Ph, R^3 = H)	15	**15a**	>99	94:6	97
2	**14b** (R^2 = 2-$NO_2C_6H_4$, R^3 = H)	8	**15b**	98	96:4	96
3[e]	**14b** (R^2 = 2-$NO_2C_6H_4$, R^3 = H)	24	**15b**	98	96:4	96
4	**14c** (R^2 = 4-$NO_2C_6H_4$, R^3 = H)	8	**15c**	99	93:7	95
5[e]	**14c** (R^2 = 4-$NO_2C_6H_4$, R^3 = H)	24	**15c**	99	93:7	95
6	**14d** (R^2 = 2-$MeOC_6H_4$, R^3 = H)	48	**15d**	92	90:10	91
7	**14e** (R^2 = 4-$MeOC_6H_4$, R^3 = H)	48	**15e**	91	89:11	93
8	**14f** (R^2 = 4-AcO,3-$MeOC_6H_3$, R^3 = H)	36	**15f**	97	93:7	97
9[f]	**14g** (R^2 = Ph, R^3 = Me)	96	**15g**	74	>99:1	88
10	**14h** 	36	**15h**	77	65:35	91, 95[g]

[a] Reaction conditions: 0.3 mmol of **13a** and 0.2 mmol of **14** in 0.2 mL of CH_2Cl_2 with 1 mol% of **BnCPN**. [b] Yield refers to isolated yield after column chromatography. [c] *dr* refers to *diastereomeric ratio* determined after short column chromatography. [d] *ee* refers to *enantiomeric excess* of major diastereomer. [e] 0.5 mol% of catalyst was used. [f] 5 mol% of catalyst was used. [g] *ee* of minor diastereomer.

After successful screening of various nitrodiene derivatives, different cyclic β-ketoesters were screened using 1 mol% of **BnCPN** as catalyst (Table 13). The five membered cyclic β-ketoesters such as methyl (**13b**), *iso*-propyl (**13c**), *tert*-butyl (**13d**) and benzyl (**13e**) β-ketoesters react with **14a** to provide respective adducts (**15i**, **15j**, **15k** and **15m**) in good to high yield (88-99%) and high stereoselectivity (88:12-97:3 *dr* and 90-97% *ee*) (entries 1-3 and 5, Table 13).

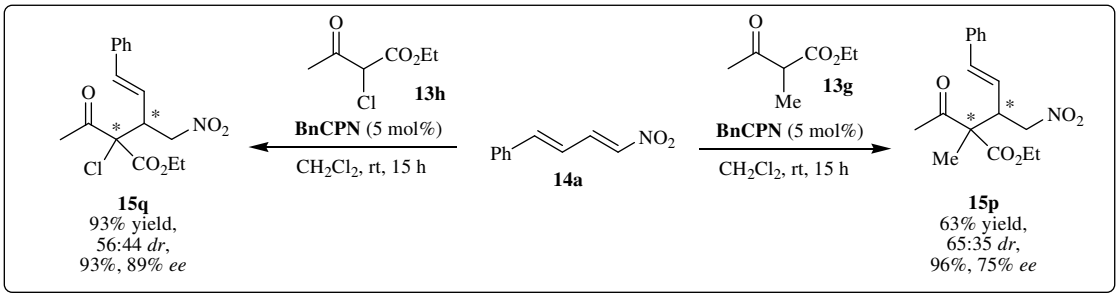
Table 13 BnCPN catalyzed asymmetric Michael reaction of β-ketoesters (**13**) with nitrodienes (**14**).[a]



Entry	13 (R^1, n)	14	Time [h]	15	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**13b** (R^1 = Me, n = 1)	**14a**	18	**15i**	99	89:11	90
2	**13c** (R^1 = *i*-Pr, n = 1)	**14a**	60	**15j**	88	96:4	93
3	**13d** (R^1= *t*-Bu, n = 1)	**14a**	72	**15k**	92	97:3	97
4	**13d** (R^1 = *t*-Bu, n = 1)	**14e**	96	**15l**	80	98:2	98
5	**13e** (R^1 = Bn, n = 1)	**14a**	48	**15m**	94	88:12	95
6	**13f** (R^1 = Et, n = 2)	**14a**	72	**15n**	82	99:1	99
7	**13f** (R^1 = Et, n = 2)	**14e**	96	**15o**	73	99:1	98

[a] Reaction conditions: 0.3 mmol of **13** and 0.2 mmol of **14** in 0.2 mL of CH_2Cl_2 with 1 mol% of **BnCPN**. [b] Yield refers to isolated yield after column chromatography. [c] *dr* refers to *diastereomeric ratio* determined after short column chromatography. [d] *ee* refers to *enantiomeric excess* of major diastereomer.

Michael addition reaction of slow reacting acyclic tri-substituted β-ketoester (**13g**) with **14a** catalyzed by 5 mol% of **BnCPN** provides the desired adduct (**15p**) in 63% yield, 63:35 *dr* and high enantioselectivity of 96% *ee* (major diastereomer) and 75% *ee* (minor diastereomer) (**Scheme 5**).



Scheme 5 Asymmetric Michael reaction of acyclic tri-substituted β-ketoesters with nitrodiene.

It is important to note that lowering of catalyst loading of **BnCPN** (1-0.05 mol%) has no effect on the enantioselectivity and diastereoselectivity of the Michael product (**15a**). Further, these results indicate a high turnover number of **BnCPN** for this transformation (Table 15). In general, turnover number (TON) of the organocatalytic reactions are lower than those of transition metal mediated processes. High catalyst turnover render this transformation ideal for industrial applications.

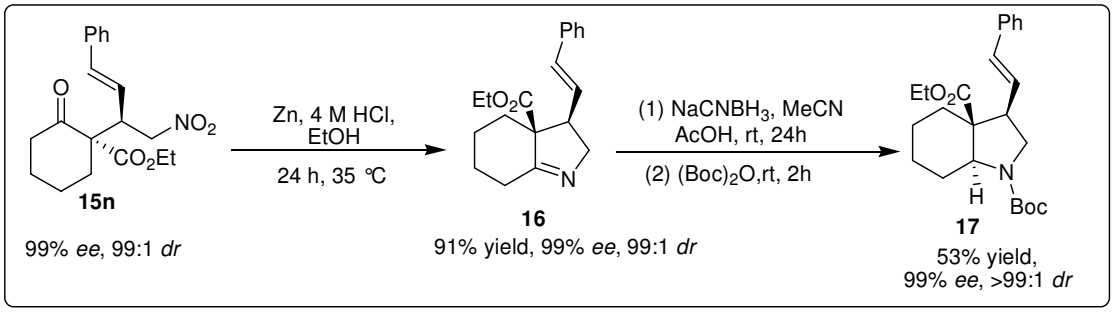
Table 15 Effect of catalyst loading.[a]

Entry	BnCPN [mol %]	Time [h]	Yield [%][b]	*dr* [c]	*ee* [%][d]	TON [e]
1	1	15	99	94:6	97	9,900
2	0.75	24	99	94:6	97	13,200
3	0.50	36	99	94:6	97	19,800
4	0.25	96	81	94:6	97	32,400
5	0.10	120	35	94:6	96	35,000
6	0.05	144	18	94:6	96	36,000

[a] Reaction conditions: 0.3 mmol of **13a** and 0.2 mmol of **14a** in 0.2 mL of CH_2Cl_2 with **BnCPN** as catalyst at rt. [b] Yield refers to isolated yield after column chromatography. [c] *dr* refers to *diastereomeric ratio* determined after short column chromatography. [d] *ee* refers to *enantiomeric excess* of major diastereomer. [e] Turnover number (**TON**) was calculated as: **TON** = yield [%] × mmol of **14a**/mmol of **BnCPN**.

The synthetic utility of this transformation was demonstrated for the synthesis of chiral octahydroindole derivative (**17**) (**Scheme 6**), since the octahydroindole is the common core in bioactive natural products such as aeruginosin 298A, dysinosin A1 and oscillarin.[12] The process involves the Zn/HCl mediated reductive cyclization of adduct **15n** to provide imine **16**. The reduction of imine (**16**) with $NaCNBH_3$ results in diastereoselective formation of octahydroindole derivative, since the hydride is preferably delivered *trans* to the carbethoxy group.

[12] a) M. Murakami, Y. Okita, H. Matsuda, H. Okino, K. Yamaguchi, *Tetrahedron Lett.* **1994**, *35,* 3129; b) J. L. R. Steiner, M. Murakami, A. Tulinsky, *J. Am. Chem. Soc.* **1998**, *120*, 597; c) S. Hanessian, R. Margarita, A. Hall, S. Johnstone, M. Tremblay, L. Parlanti, *J. Am. Chem. Soc.* **2002**, *124*, 13342; d) S. Hanessian, M. Tremblay, J. F. W. Petersen, *J. Am. Chem. Soc.* **2004**, *126*, 6064.



Scheme 6 Derivatization of Michael adducts (**15n**) to octahydroindole carboxylate (**17**).

It was proposed that 9-*O*-benzylcupreine (**BnCPN**) or 9-*O*-benzylcupreidine (**BnCPD**) acts as bifunctional organocatalyst, providing synergic activation to both the reactants. The proposed transition state involves a ternary complex of β-ketoester, nitrodiene and catalyst. The quinuclidine nitrogen of the catalyst activate the nucleophile by stabilizing the enol through hydrogen bonding and the aromatic OH of the catalyst activate the nitrodiene and also orient the ketoester with hydrogen bonding network (**Figure 9**).

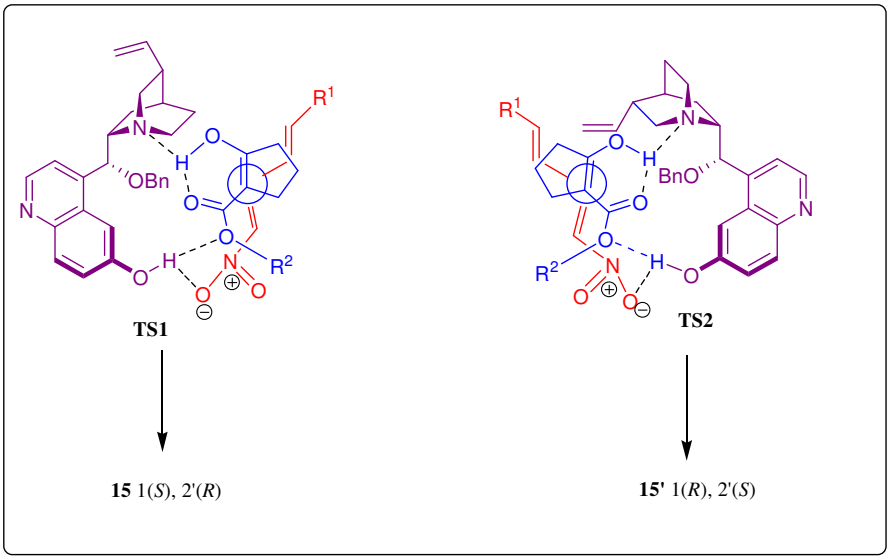


Figure 9 Plausible transition state: **TS1** with **BnCPN** and **TS2** with **BnCPD**.

Friedel-Crafts reaction of indoles with electron deficient olefins using water compatible organocatalyst

In recent years, the organic chemists are faced with the challenge of developing environmentally friendly and economical chemical processes. On the other hand, the development of chemical reaction by the application of Brønsted acid as mild, cost effective,

commercially available and highly efficient organocatalyst has attracted much attention in recent years for being environmentally benign non-asymmetric as well as asymmetric process. The Brønsted acid catalysis in water provides a green catalytic procedure for synthetic organic transformation. Recently, Yao and co-workers have reported catalyst free aqueous-mediated conjugative addition of indoles to nitroalkenes at high temperature providing access to Friedel-Crafts product in moderate to good yield. In continuation of the interest of developing green methodologies for asymmetric and non-asymmetric transformations, the application of D-camphorsulfonic acid (D-CSA) as an efficient catalyst for Michael type Friedel-Crafts addition of indoles to nitro-olefins and enones in water is reported.

Initially, the reaction of indole **19a** with *trans* β-nitrostyrene **20a** in the presence of different water soluble Brønsted acids as catalysts were carried out (**Table 16**). The screening of different protic acids shows that except for triflic acid (**Table 16**, entry **9**) all sulfonic acids give better yield as compared to other protic acids, and amongst them D-CSA provides the product **21aa** in highest yield of 88% (**Table 16**, entry 6). The optimization of the reaction conditions shows that lowering the volume of water to 1.5 mL affords the product in 93% yield (**Table 16**, entry 11). Further decrease in the amount of water makes the stirring difficult and leads to lower yields of the product (**Table 16**, entry 13). Reducing the catalyst loading decreases the rate of the reaction (**Table 16**, entry 12). The use of protic solvents like ethanol (**Table 16**, entry 14) and methanol (**Table 16**, entry 15) lowers the reaction rate. In the absence of catalyst the product was formed in traces. Thus, stirring equimolar quantity of reactants in 1.5 mL of water as solvent and 20 mol % of D-CSA as catalyst at RT constitutes the optimized condition for this Michael type Friedel-Crafts reaction.

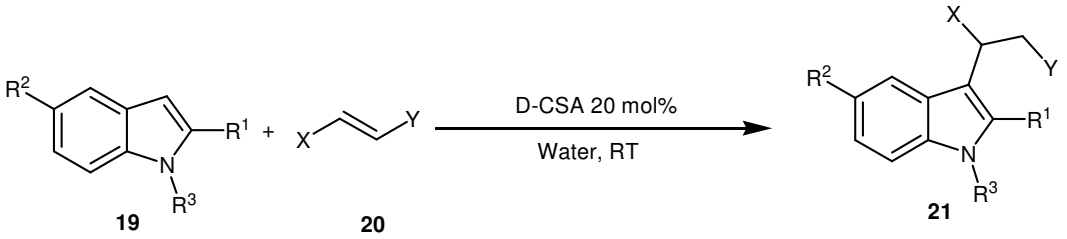
Substrate scope: In order to extend the scope of this method, the conjugate addition of indole derivative to varieties of nitro-olefins and enones were carried out under optimized reaction conditions (**Scheme 7**). This may provide a convenient synthetic process for the functionlization of the 3-position of indole with nitroethyl group, which can be used as a building block for the synthesis of biomolecules. Nitrostyrene possessing electron withdrawing group gives higher yield of the addition products for example in the reaction of indole **19a** with 4-fluoro- **20b**, 4-chloro- **20c** and 3-nitro-(β-nitrostyrene) **20d** afford the

addition product in 95%, 94% and 93%, respectively (**Table 17,** entry 2-4). 3-Nitro-(β-nitrostyrene) **20d** reacts faster (8 hr) as compared to **20b** and **20c**. The substituents on indole ring also affect the reaction rate. The electron rich indoles such as 5-methoxy indole **19c** react with nitro-olefins in a shorter reaction time (8 hr) to provide the addition product in high yield (**Table 17,** entry 9-14). 2-Methylindole **19b** with nitro-olefins underwent smooth reaction providing adduct in high yield (**Table 17,** entry 17-22). 1-Methylindole **19d** however, reacted slowly under the reaction condition.

Table 15-Catalyst screening and optimization[a].

Entry	Catalyst	Solvent (mL)	Yield (%)[b]
1	-	H_2O (2.0)	Traces
2	CH_3COOH	H_2O (2.0)	42
3	TFA	H_2O (2.0)	72
4	HCl	H_2O (2.0)	Traces
5	*p*-TsOH	H_2O (2.0)	78
6	D-CSA	H_2O (2.0)	88
7	4-$NH_2C_6H_4SO_3H$	H_2O (2.0)	75
8	$ClSO_3H$	H_2O (2.0)	72
9	TfOH	H_2O (2.0)	38
10	D-CSA	H_2O (1.0)	92
11	D-CSA	H_2O (1.5)	93
12	D-CSA	H_2O (1.5)	68[c]
13	D-CSA	H_2O (0.1)	76
14	D-CSA	EtOH (2.0)	36
15	D-CSA	MeOH (2.0)	55

[a]All reactions were carried out with 0.5 mmol of indole and 0.5 mmol of *trans* β-nitrostyrene, [b]Yield refers to isolated yield after column chromatography, [c]10 mol% of catalyst was used.



19a. $R^1 = R^2 = R^3 = H$; **19b.** R^1 = Me, $R^2 = R^3 = H$; **19c.** $R^1 = R^3 = H$, R^2 = OMe; **19d.** $R^1 = R^2 = H$, R^3 = Me.

20a. X = Ph, Y = NO_2; **20b.** X = 4-FPh, Y = NO_2; **20c.** X = 4-ClPh, Y = NO_2; **20d.** X = 3-NO_2Ph, Y = NO_2; **20e.** X = 4-MeOPh, Y = NO_2; **20f.** X = furyl, Y = NO_2; **20g.** X = Ph, Y = COMe; **20h.** X = Ph, Y = COPh.

Scheme 7 -D-CSA catalyzed Friedel-Crafts reaction of indole derivatives with electron deficient olefins.

Table 17-Substrate scope:

Entry	Indoles **19**	Olefins **20**	Products **21**	Time (hr)	Yield (%)[a]
1	**19a**	**20a**	**21aa**	10	93
2		**20b**	**21ab**	10	95
3		**20c**	**21ac**	10	94
4		**20d**	**21ad**	8	93
5		**20e**	**21ae**	15	81
6		**20f**	**21af**	10	86
7		**20g**	**21ag**	10	81
8		**20h**	**21ah**	24	73
9	**19b**	**20a**	**21ba**	10	90
10		**20b**	**21bb**	10	98
11		**20c**	**21bc**	10	97
12		**20d**	**21bd**	10	97
13		**20e**	**21be**	15	88
14		**20f**	**21bf**	10	94
15		**20g**	**21bg**	10	78
16		**20h**	**21bh**	24	83
17	**19c**	**20a**	**21ca**	8	94
18		**20b**	**21cb**	8	93
19		**20c**	**21cc**	8	90
20		**20d**	**21cd**	8	92
21		**20e**	**21ce**	15	82
22		**20f**	**21cf**	8	86
23		**20g**	**21cg**	10	71
24		**20h**	**21ch**	24	77
25	**1d**	**20a**	**21da**	24,12,12	81, 83[b], 35[c]
26		**20b**	**21db**	24, 12	86, 86 [b]
27		**20c**	**21dc**	24, 12	85, 89 [b]
28		**20d**	**21dd**	24, 12	85, 87 [b]
29		**20e**	**21de**	24, 15	75, 80 [b]
30		**20f**	**21df**	24, 12	77, 86 [b]
31		**20g**	**21dg**	24, 12	NR[d], 74 [b]
32		**20h**	**21dh**	24, 12	NR[d], 78 [b]

[a]Yield refers to isolated yield after column chromatography. [b]Reactions were carried in 0.1 mL of water. [c]Reaction carried out under neat condition. [d]No reaction under standard reaction conditions.

Annexure II

Summary of the project

In this project we have developed environmentally benign Friedel-Crafts and *aza* Friedel-Crafts reaction for the construction of chiral 3-indolyl-3-hydroxyindole and chiral aminonapthols which are present in many bioactive natural products, pharmaceutically active compounds and chiral auxillaries in asymmetric synthesis using natural *Cinchona* alkaloid and modified *Cinchona* alkaloid as organocatalyst. The scope of these reactions has also been explored. The 3-indolyl-3-hydroxyindole and aminonapthols have been obtained in excellent yield up to 98% and as well as excellent enantioselectivity up to 99%. A highly stereoselective approach for the construction of vicinal quaternary and tertiary stereocenters *via* 9-*O*-benzylcupreine (**BnCPN**) or 9-*O*-benzylcupreidine (**BnCPD**) catalyzed Michael addition of tri-substituted carbon nucleophiles to nitrodienes has been developed. This methodology is not only applicable to a wide variety of carbon nucleophiles but also successful to a substantial range of nitrodienes as well. A high turnover number of the catalyst enables the successful scaling up of the reaction. The product can be readily converted into chiral octahydroindole analogue which, further enhance the utility of this transformation for the synthesis of potentially valuable chiral molecules.

Annexure III

Publications

1. Asymmetric Addition of Indoles to Isatins Catalysed by Bifunctional Modified Cinchona Alkaloid Catalysts. P Chauhan, S S Chimni *Chemistry: A European Journal* **2010**, *16*, 7709-7713.
2. Asymmetric Organocatalytic aza-Friedel-Crafts Reaction of Naphthols with N-Sulfonyl Imines. P. Chauhan, S. S. Chimni *Eur. J. Org. Chem.* **2011**, 1636–1640.
3. Catalyst-free and Solventless Hantzsch Ester Mediated Reduction of Nitroolefins at Elevated Temperature. P. Chauhan, K. Kaur. N. Bala, V. Kumar, S. S. Chimni *Indian J. Chemistry*. **2011**, *50B*, 304-309.
4. Facile Construction of Vicinal Quaternary and Tertiary Stereocenters via Regio- and Stereoselective Organocatalytic Michael Addition to Nitrodienes. P Chauhan, S S Chimni *Adv. Synth. Catal.* **2011**, *353*, 3202-3212.
5. Aromatic Hydroxyl Group - A Hydrogen Bonding Activator in Bifunctional Asymmetric Organocatalysis. P Chauhan, S S Chimni *RSC Advances* **2012**, *2*, 737-758.(Review)
6. Recent advances in asymmetric organocatalytic conjugate addition of arenes and hetero-arenes. P Chauhan, S S Chimni *RSC Advances* **2012**, *2*, 6117 – 6134. (Review)