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Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701238

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701238

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Organoocatalytic Asymmetric [4 + 2] Cycloaddition of 1-Acetylcyclopentene and 1-Acetylcyclohexene for the Synthesis of Fused Carbocycles

Utpal Nath and Subhas Chandra Pan*[a]

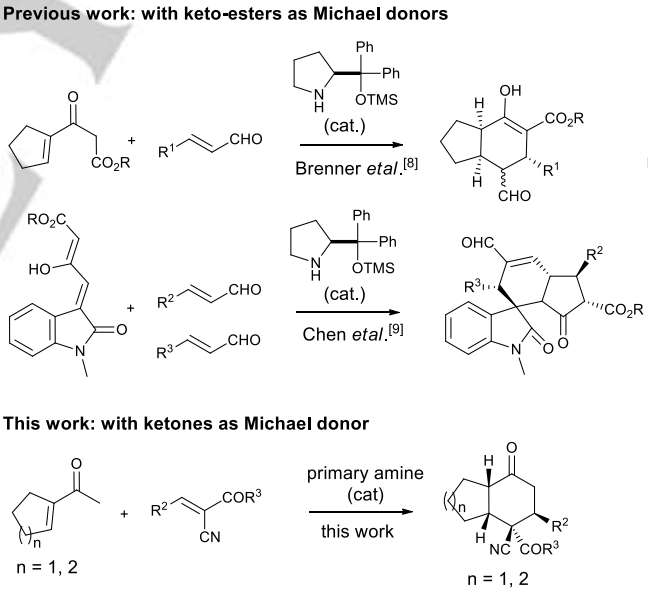
Dedication ((optional))

Abstract: The first organocatalytic asymmetric [4+2] cycloaddition reaction employing 1-acetylcyclopentene and 1-acetylcyclohexene is described. Enones having cyano group are used as the dienophile partner in this method. The reaction provides a useful practical route for the synthesis of bicyclic fused carbocycles having four contiguous stereocentres.

The Diels−Alder (DA) reaction is considered as one of the most commanding, practical, and elegant synthetic approaches in organic chemistry, which exhibits plentiful applications in the total synthesis of natural products and drugs.[1] In recent years dienamine[2] catalytic cycloaddition/cyclization[3] reactions has proven to be a powerful method for the construction of cyclic molecules. In particular, after the initial discovery by Barbas and co-workers, cross-dienamines derived from *α*, *β*-unsaturated ketones have been exploited tremendously with a range of electrophiles.[4] Though this method was applied for the synthesis of a variety of carbocycles and heterocycles, to the best of our knowledge, it has not been used for the synthesis of fused carbocycles.

Fused organic moieties such as 1-decalone, 1-decalin and octahydro-1*H*-indene are present in a wide range of bioactive compounds[5] such as Rapiculine,[5a] Brasilanes,[5b] Conocephalenols[5c] etc. Thus it is highly desirable to prepare these compounds in economical and direct way. In 2005, MacMillan and co-workers developed an iminium catalytic intramolecular Diels-Alder reaction for the synthesis of fused carbocycles and heterocycles.[6] Later in 2008, Christmann *et al.* demonstrated dienamine catalytic intramolecular cyclization of tethered *α*, *β*-unsaturated aldehydes for the synthesis of fused structures.[7] Brenner and McGarraugh reported intermolecular synthesis of hexahydro-1*H*-indene motif *via* double Michael reaction between enals and *β*-ketoesters having cyclopentene moiety (Scheme 1).[8] Also, Chen and co-workers applied aminocatalytic domino strategy for the synthesis of fused carbocycles with spirooxindole motif (Scheme 1).[9] We also recently reported[10] a stepwise synthesis of 1-decalone and hexahydro-1*H*-inden-4(2*H*)-one structures *via* dienamine catalytic Michael reaction followed by 1,1,3,3-tetramethylguanidine mediated cyclization where 1-acetylcyclohexene and 1- acetylcyclopentene were employed; however the products were obtained in moderate enantioselectivities. Realizing the importance of fused carbocyclic structures for the synthesis of bioactive compounds, we embarked in direct synthesis of fused carbocycles utilizing 1-acetylcyclopentene and 1-acetylcyclohexene. We envisaged that strong dienophiles could undergo [4+2]-cycloaddition reaction providing fused carbocycles. In this regard, we planned to use electron poor olefins having cyano and keto group attached to it (Scheme 1).

Scheme 1. Organocatalytic intermolecular asymmetric synthesis of fused carbocycles



Inspired by these thoughts, the investigation was started by mixing 1-acetylcyclopentene (**1a**, 0.05 mmol), enone **2a** (0.05 mmol), quinidine derived primary amine **I** (20 mol%) and 2-fluorobenzoic acid (20 mol%) as co-catalyst in dichloromethane as the solvent.[11] To our delight, after stirring at room temperature for 7 days, the desired major fused bicyclic product 4-benzoyl-7-oxo-5-phenyloctahydro-1*H*-indene-4-carbonitrile (**3a)** was obtained in 70% yield with 11:1 diastereomeric ratio and 59% ee (Table 1, entry 1). Interestingly, the enantiomeric excess got enhanced to 84% by employing *epi*-cinchonine amine **II** (entry 2). Though slightly higher enantioselectivity was achieved with hydroquinine derived catalyst **III** (entry 3) but the enantioselecti-

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[b] This work is supported by DST-MPI partner programme. We thank CIF of Indian Institute of Technology Guwahati for the instrumental facility.

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10.1002/ejoc.201701238

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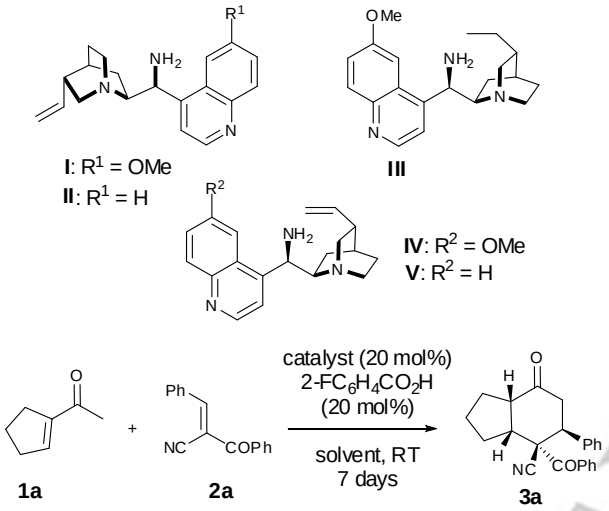
vity dropped using quinine derived amine **IV** (entry 4). Pleasingly, cinchonidine derived amine catalyst **V** delivered the product **3a** in 6:1 diastereomeric ratio with 94% ee (entry 5). Then, to further improve the diastereo- and enantioselectivity of the reaction, different solvents were screened (entries 6-8). An enantiomeric excess of 96% was achieved with α,α,α-trifluoro toluene as the solvent (entry 7). Finally, the best solvent turned out to be toluene and the product **3a** was isolated in 87% yield with 13:1 dr and 96% ee (entry 8). The enantioselectivity dropped to 92% when a higher amount of co-catalyst 2-fluorobenzoic acid was used (entry 9).

Table 1: Optimization of the reaction condition

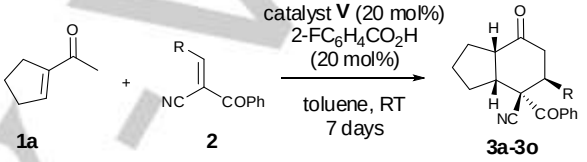


Entry[a]	Catalyst	Solvent	Yield[b]	d.r[c]	ee[d]
1	**I**	CH_2Cl_2	70	11:1	59
2	**II**	CH_2Cl_2	65	7:1	84
3	**III**	CH_2Cl_2	68	6:1	89
4	**IV**	CH_2Cl_2	72	3.2:1	76
5	**V**	CH_2Cl_2	72	6:1	94
6	**V**	mesitylene	81	9:1	94
7	**V**	$PhCF_3$	83	6:1	96
8	**V**	toluene	87	13:1	96
9[e]	**V**	toluene	88	13:1	92

[a] All reactions were carried out with 0.05 mmol of **1a** with 0.05 mmol of **2a** in 0.5 ml solvent 20 mol% catalyst and 20 mol% 2-$FC_6H_4CO_2H$ at RT for 7 days. [b] Isolated yield after silica gel column chromatography. [c] Determined by 1H nmr. [d] Determined by chiral HPLC and of the major diastereomer. [e] With 30 mol% 2-$FC_6H_4CO_2H$.

After finalizing the optimized conditions the scope of the reaction was studied. Initially different enones **2** having variations of the substitutions on the aryl group of the double bond was investigated (Table 2). It turned out that a variety of electron donating, electron neutral and electron withdrawing substitutions are well tolerated in our reaction condition. Different *para*-substituted *β*-aryl enones were initially employed in the reaction and excellent results were achieved (entries 2-9). For example, products **3b** and **3c** having 4-methyl and 4-propan-2-yl substitutions were isolated in high enantioselectivities and interestingly higher diastereomeric ratio was obtained for product **3c** (entries 2-3). Also products **3e**-**3g** having different 4-halo substitutions were obtained in high diastereo- and enantioselectivities (entries 5-7). Biphenyl substituted enone **2h** also participated in the reaction delivering product **3h** in 94% ee (entry 8). High diastereo- and enantioselectivity was also observed for product **3i** having *para*-nitro substitution, however the yield was moderate (entry 9). Then *ortho*- and *meta*-substituted enones **2j** and **2k** were employed in the reaction and

Table 2: Scope of enone with varied olefin substituents



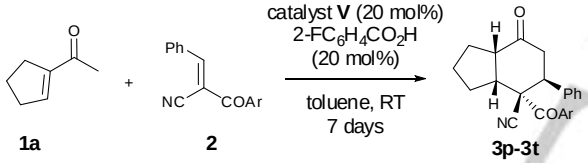
Entry[a]	R	Product	Yield[b]	dr[c]	ee[%][d]
1	Ph	**3a**	87	13:1	96
2	4-MeC_6H_4	**3b**	72	13:1	96
3	4-$iPrC_6H_4$	**3c**	67	>20:1	95
4	4-$OMeC_6H_4$	**3d**	60	10:1	93
5	4-FC_6H_4	**3e**	89	17:1	98
6	4-ClC_6H_4	**3f**	69	>20:1	97
7	4-BrC_6H_4	**3g**	87	19:1	98
8	4-PhC_6H_4	**3h**	81	16:1	94
9	4-$NO_2C_6H_4$	**3i**	39	>20:1	94
10	3-MeC_6H_4	**3j**	83	13:1	94
11	2-MeC_6H_4	**3k**	65	9:1	92
12	1-Naphthyl	**3l**	60	8:1	83
13	2,4-$Cl_2C_6H_3$	**3m**	55	15:1	82
14	Thiophen-2-yl	**3n**	52	6:1	76
15	(*E*)-Ph-CH=CH-	**3o**	40	5.2:1	>99

[a] Unless otherwise mentioned, reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2** in 1 ml toluene using 20 mol% **V** and 20 mol% 2-$FC_6H_4CO_2H$ at RT for 7 days. [b] Isolated yield after silica gel column chromatography. [c] Determined ^1H NMR. [d] Determined by chiral HPLC and of the major diastereomer.

delightfully the outcome was good (entries 10-11). The reaction also progressed well with enone **2l** having 1-naphthyl group and slight less enenatioselectivity was detected (entry 12). A disubstituted aryl group containing enone was also tolerated in our reaction displaying good result (entry 13).Importantly, enone **2n** having thiophen-2-yl moiety could also be a good substrate in the reaction *albeit* slight lesser enantioselectivity was observed (entry 14). Finally, cinnamyl group containing enone **2o** was screened and excellent enantioselectivity was attained for the corresponding product **3o** (entry 15). Cyclohexyl substituted enone was also screened but trace amount of product formation was observed even after 15 days of stirring.

Next, the ketone functionality of the enone was varied and the results are summarized in Table 3. Here also, different substitutions on the phenyl group of ketone were tolerated and excellent results were obtained. Initially, *para*-substituted enones having electron donating groups were screened and interestingly higher enantioselectivity was detected for product **3p** than **3q** (entries 1-2). Additionally, the outcome was also excellent with 4-halo substituted enones **2r**-**2s** (entries 3-4). Finally a *meta*-substituted enone was engaged in the reaction and the product **3t** was obtained in high diastereo- and enantioselectivity (entry 5). Acetyl substituted enone did not provide any product at room temperature as well as at elevated temperature.

Table 3: Scope of enone with varied ketone substituents



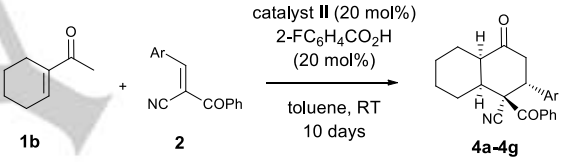
Entry[a]	Ar	Product	Yield[b]	dr[c]	ee[%][d]
1	4-MeC_6H_4	**3p**	88	17:1	94
2	4-$OMeC_6H_4$	**3q**	64	20:1	93
3	4-ClC_6H_4	**3r**	72	12:1	94
4	4-BrC_6H_4	**3s**	54	10:1	95
5	3-ClC_6H_4	**3t**	66	8:1	96

[a] Unless otherwise mentioned, reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2** in 1 ml toluene using 20 mol% **V** and 20 mol% 2-$FC_6H_4CO_2H$ at RT for 7 days. [b] Isolated yield after silica gel column chromatography. [c] Determined ^1H NMR. [d] Determined by chiral HPLC and

Then we became interested to employ 1-acetylcyclohexene (**1b**) in our cycloaddition reaction. Initially, the reaction between **1b** and enone **2a** was investigated using cinchoinidine catalyst in combination with 2-F benzoic acid. The reaction was found to be slower than with **1a**; and gratifyingly the cyclized 1-decalone product **4a** was obtained in 7:1 dr with 96 % ee. Heating the reaction mixture was not beneficial as it provided some undesired mixtures of products. After some optimization, it was found that cinchonine derived primary amine **II** could provide the product **4a** in same diastereomeric ratio with 99% ee at room temperature. The enantiomeric ratio for the minor diastereomer was also 99%. Under this conditions, different enones having variations in the aryl group of olefin were screened (see supporting information for details).

Gratifyingly, as can be seen in Table 4, the products were obtained in high enantioselectivities irrespective of the nature of the substitutions on the aryl group. Initially, different *para*-substitions were screened and good results were observed. For instance, **1b** on reaction with **2b** furnished the corresponding cyclized product **4b** in 5:1 dr with 90% ee (entry 2). Similarly different *para*-halo substitutions were tolarated in the reaction providing product **4c** in high enantioselectivity (entry 3). The reaction was sluggish with enone **2h** having biphenyl moiety but the enantiomeric excess of the corresponding product **4d** was excellent (entry 4). Besides *meta*-substituted enones were also found to be good partner in this reaction and highest diastereoselectivity (9:1 dr) was attained for product **4f** (entry 6). Finally slight slow reactivity was observed for an *ortho*-substituted enone **2k** delivering product **4g** in 17% yield with 1.6:1 dr and 89% ee for the major and >99% for the minor (entry 7).

Table 4. Scope of enone having varied olefin substituents with 1-acetyl cyclohexene



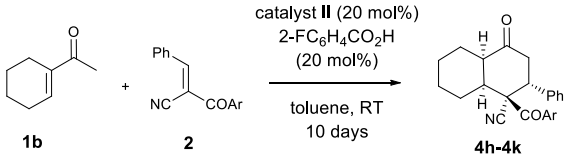
Entry[a]	Ar	Product	Yield[b]	dr[c]	ee[%][d]
1	Ph	**4a**	34	7:1	99
2	4-MeC_6H_4	**4b**	25	5:1	96
3	4-BrC_6H_4	**4c**	22	4:1	96
4	4-PhC_6H_4	**4d**	15	4:1	95
5	3-MeC_6H_4	**4e**	28	4:1	95
6	3-BrC_6H_4	**4f**	26	9:1	95
7	2-MeC_6H_4	**4g**	17	1.6:1	89(>99)

[a] Unless otherwise mentioned, reactions were carried out with 0.15 mmol of **1b** with 0.15 mmol of **2** in 1.5 ml solvent using 20 mol% **V** and 20 mol% 2-$FC_6H_4CO_2H$ at RT for 10 days. [b] Combined yield of the isolated product. [c] Diastereoselectivity was determined by ^1H NMR. [d] Enantioselectivity was determined by chiral HPLC and of the major diastereomer, the ee of minor diastereomer is given in the parenthesis.

The generality of the reaction was further demonstrated by employing enones with varied keto functionalities (Table 5). Gratifyingly, the reaction condition was also found to be suitable for the enones having different keto functionalities. Though good diastereoselectivity was achieved for product **4h** (entry 1), inferior

diastereoselectivity was detected for the products **4i**-**4j** derived from enones **2r-2s** (entries 2-3). But the enantioselectivity for both the diastereomer using **2s** were very good. A *meta*-substitutted enone reacted slowly and less yield but high enantioselectivity was observed for the corresponding product **4k** (entry 4).

Table 5. Scope of enone having varied keto substituents with 1-acetyl cyclohexene

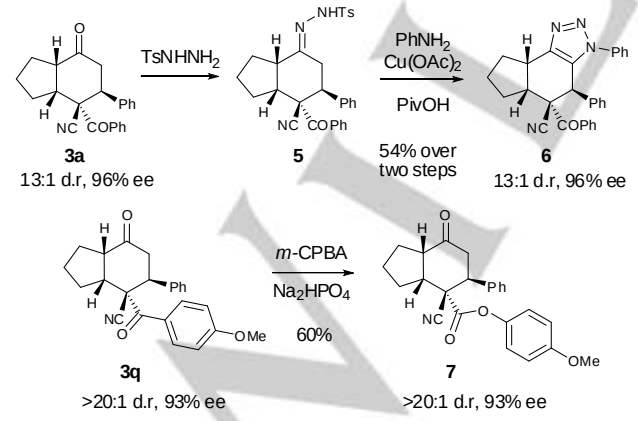


Entry[a]	Ar	Product	Yield[b]	dr[c]	ee[%][d]
1	4-MeC$_6$H$_4$	**4h**	22	8:1	94
2	4-ClC$_6$H$_4$	**4i**	26	2:1	90 (56%)
3	4-BrC$_6$H$_4$	**4j**	28	1.6:1	>99 (93%)
4	3-ClC$_6$H$_4$	**4k**	17	4:1	99

[a] Unless otherwise mentioned, reactions were carried out with 0.15 mmol of **1b** with 0.15 mmol of **2** in 1.5 ml solvent using 20 mol% **V** and 20 mol% 2-FC$_6$H$_4$CO$_2$H at RT for 10 days. [b] Combined yield of the isolated product. [c] Diastereoselectivity was determined by ^{1}H NMR. [d] Enantioselectivity was determined by chiral HPLC and of the major diastereomer.

To illustrate the utility of our method, few reactions were carried out on **3a** and **3q** (Scheme 2). Initially copper mediated triazole synthesis[12] was envisaged from **3a**. For this, first **3a** was converted to tosylhydrazone **5** which upon treatment with aniline, copper acetate and pivalic acid delivered triazole **6** in 54% overall

Scheme 2: Synthetic transformation of **3a** and **3q**



yield. It is delighting that both the diastereo- and enantiopurity got retained in this process (Scheme 2). Then a Baeyer Villiger oxidation reaction was performed on **3q** having a 4-anisyl group. The reaction progressed smoothly affording the ester product **7** in 60% yield and here also both diastereo- and enantioselectivity got preserved.

The absolute configuration of product **3f** was assigned to be (3*aR*,4*R*,5*S*,7*aS*) by X-ray crystallography.[13] The absolute structure of other products **3** are expected to be same by analogy. Also, the absolute structure of product **4** can be proposed to be opposite as cinchonine and cinchonidine used to provide enantiomeric products.[14]

In summary, we have developed the first catalytic asymmetric [4+2]-cycloaddition reaction of 1-acetylcyclopentene and 1-acetylcyclohexene providing bicyclic fused frameworks. Electron deficient olefins having simultaneous cyano and keto groups were identified as the most suitable dienophile and cinchona alkaloid derived primary amines were found to be the best catalysts. The bicyclic products having four contiguous stereogenic centres including one quaternary centre are obtained in high diastereo- and enantioselectivities and also valuable synthetic transformations including triazole synthesis has been demonstrated. Thus our methodology is useful to prepare such bicyclic skeletons in a simple and efficient way.

Experimental Section

General procedure for the formation of **3a**-**3t**: In a 5 ml round bottomed flusk enone **2** (0.1 mmols), *epi*-cinchonidine amine **V** (20 mol%, 0.02 mmols, 5.9 mg), 2-fluoro benzoic acid (20 mol%, 0.02 mmols, 2.8 mg) was taken and 1-aectyl cyclopentene (0.1 mmols, 11 mg) and 1 mL toluene was added and the reaction mixture was stirred at room temperaure for 7 days. The reaction mixture then directly employed to column chromatographic separation using 4% ethyl acetate/hexane as eluent to obtain pure product **3**.

General procedure for the formation of **4a**-**4k**: In a 5ml round bottomed flusk enone **2** (0.15 mmols), *epi*-cinchonine amine **II** (20 mol%, 0.03 mmols, 8.9 mg), 2-fluoro benzoic acid (20 mol%, 0.03 mmoles, 4.2 mg) was taken and 1-aectyl cyclohexene (0.15 mmols, 18.6 mg) and 1.5 mL toluene was added and the reaction mixture was stirred at room temperaure for 10 days. The reaction mixture then directly employed to column chromatographic separation using 3% ethyl acetate/hexane as eluent to obtain pure product **4**.

Acknowledgements ((optional))

This work is supported by Board of Research in Nuclear Sciences, India, (Grant no. 2012/20/37c/05/BRNS). We also thank CIF, Indian Institute of Technology Guwahati for the instrumental facility and Gobinda Dolai for starting material preparations.

Keywords: [4+2] cycloaddition • dienamine catalysis• carbocycle• organocatalysis • enantioselecitivity

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10.1002/ejoc.201701238

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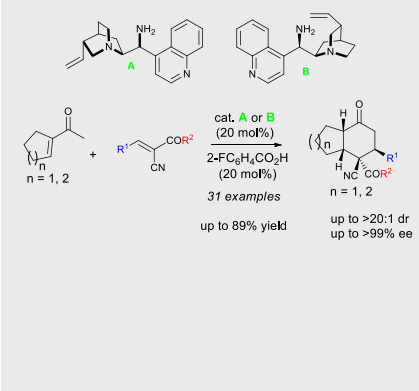
A highly diastereo- and enantioselective [4+2] cycloaddition of 1-acetylcyclopentene and 1-acetylcyclohexene with cyano group containing enones is described. With 20 mol% chiral primary amine catalyst and 2-flurobenzoic acid as additive, high yields and good to excellent enantioselectivities have been achieved.



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