SYNTHESIS OF TETRAHYDROPYRANONES WITH NANO CATALYTIC ENANTIOSELECTIVE OXA-AHETERO-DIELS ALDER REACTION OF ENONES WITH ARYL TRIFLUOROMETHYL KETONES

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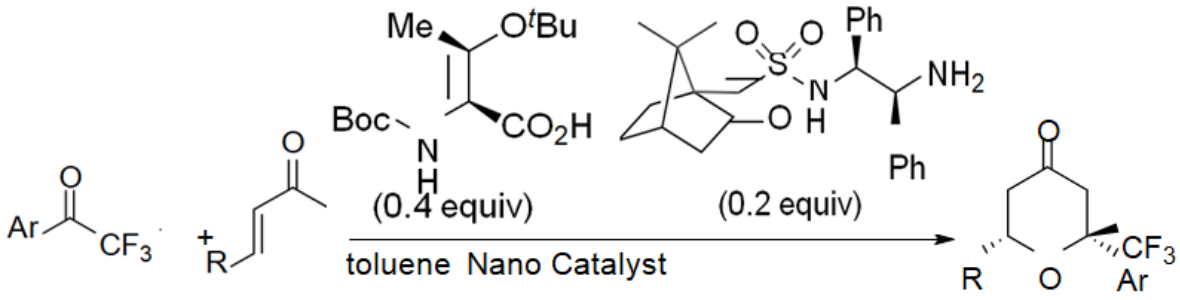
***Abstract*- The Enantioselective and Diastereo activities of oxa-hetero-Diels-Alder reactions of aryl trifluoromethyl ketones with enones that give the tetrahydropyranone derivatives are catalyzed by the system of nano amine-based catalyst are reported. The tetrahydropyranone products reactions had major diastereomers are obtained in the virtual stereochemistry different from that of the past synthesized derivatives of tetrahydropyranone.**

The Derivatives of the Tetrahydropyran are found in natural bioactive products and Leads in pharmaceuticals. succinct enantiomerically access to enrich the derivatives of tetrahydropyran are interest in the advancement of bioactive molecules.[1-3] A group of trifluoromethyl is repeatedly used to get better i n the bioactivities.[4-7] therefore, the method for the terse of synthesis of the tetrahydropyran derivatives bearing a group of trifluoromethyl are of curiosity.[1] In formerly reported of oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones that unswervingly disburse for derivatives of tetrahydropyranone are using the systems of amine-based nano catalyst.[1] In these reactions, the groups of ketone carbonyl with the aryl trifluoromethyl ketones perform as dienophiles in the [2+4] cycloadditionleading to the derivatives of tetrahydropyranone and the enamines generated from the enones act as dienes. there are two diastereomers can be formed in these reactions . Here we report enantioselective of oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones that unswervingly disburse of the other type of the diastereomers as the major products (method 1a)[1].

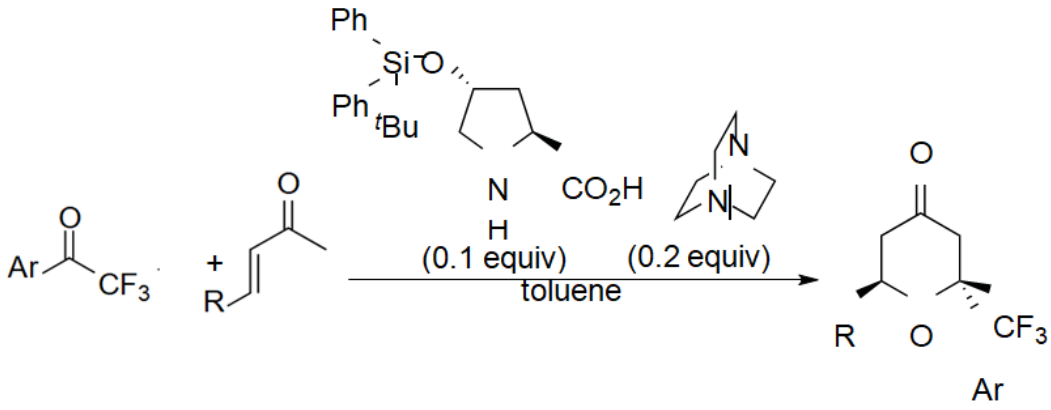
The use of a system of nano catalyst composed of a derivative of proline and DABCO for the leads of the formation of reactions one type of the diastereomers as the main diastereomers with highly enantioselectivities (method 1b).[1]

a. This work of Enone reaction



yield up to 81% (major diastereomer)
dr up to 9:1 (before purification)
dr >28:1 (after purification)
er up to 98:2 (major diastereomer)

b. Past Ketone reaction



Method 1. (a) Enantioselective oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones.(b) formerly reported in the reactions of enantioselective oxa-hetero-Diels-Alder of enones with aryl trifluoromethyl ketones. The the major diastereomers in the relative stereochemistry of the reaction shown in 1st reaction is different from that of the past obtained major diastereomers in the reactions shown in reaction completed by the presents of nano catalyst system (b).
The study of amine derivatives and the systems nano catalyst of amine-containing were tested for their abilities to catalyze the reaction of an aryl trifluoromethyl ketone with an enones to lead to the tetrahydropyranone product.[1] In several cases, particularly with primary derivatives of amine with acids, the minor diastereomer and major diastereomer of the obtained from the catalyzed reaction by the DABCO.[1] and derivative of proline. the form of aldol product in significant amounts with the tetrahydropyranone product and/or the enantioselectivities of the obtained tetrahydropyranones were relatively moderate or low.[1] We hypothesized that supplementary evaluations of 1º amine derivatives with out or with acids under different conditions.[3a-c] the identifynano catalyst by nanoparticulars in the systems proper for the oxa-hetero-Diels-Alder of affording in the reactions. the other category diastereomers of tetrahydropyranones as the major product by high diastereo- and enantioselectivities.

The Derivatives of amines were tritrated in the nanocatalysis of the reaction of 2,2,2-trifluoroacetophenone (**1a**) with enone **2a** to specified the derivative of tetrahydropyranone **3a-1** as the product of main within a high diastereo- and enantioselectivities with high yield; the results are shown in Table 1 (Completed all evaluated results will be published in the earlyas possible). The ratio between 1a,**3a**-2, its diastereomer **3a-1**, and product of aldol **4a** were determined by ^{1}H NMR analysis, and the enantiomer ratios of **3a-2** are by the determine of HPL Chromatography analysis after purification o f the catalyst systems tested, amine derivative **B**[8] with various acids
The provided attractive results. Then, using the derivative of amine **A**, the conditions of the reaction were additional evaluated from these evaluations, the used of system of nano catalyst collected of N-Boc-O-tBu-L-threonine (**A**) and amine derivative **B** as an acid in toluene at 6°C was identified as the best among those tested (Table 1, entry 8).

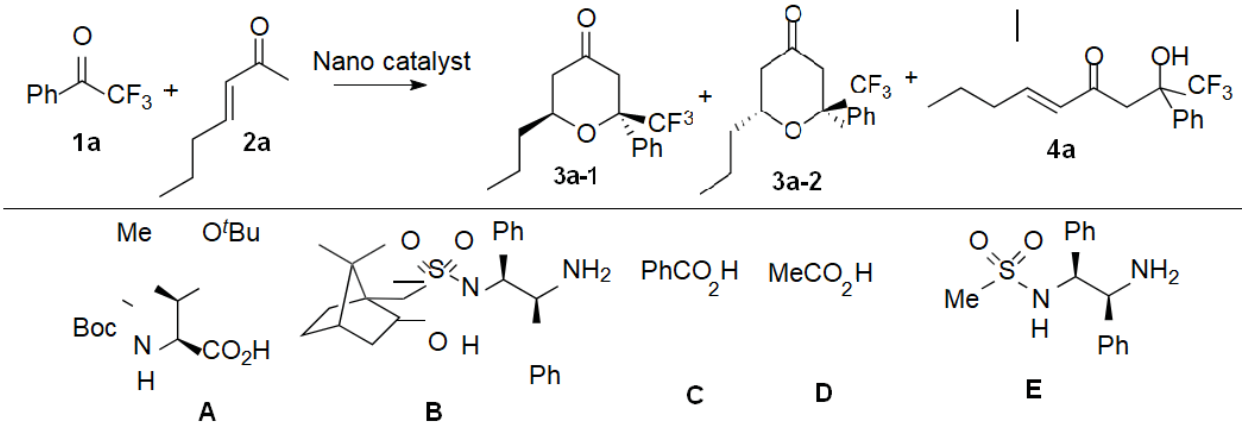


Table 1. Evaluations of catalysts and conditions

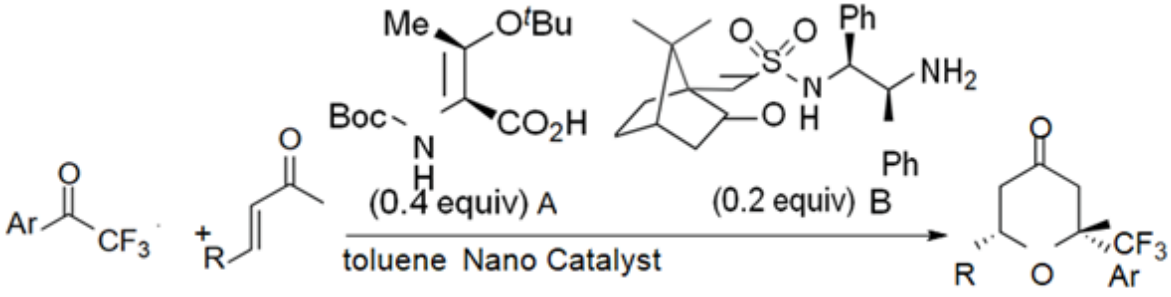
entry	catalyst system		solvent	time (h)	temp (°C)	ratio **1**:**3a**:**4a**	er of **3a-2**	dr **3a-1**:**3a-2**
	acid	amine						
1	**A**	**B**	toluene	40	26	5:80:15	85:15	6:1
2	**A**	**B**	$CHCl_3$	48	26	12:82:6	84:16	8:1
3	**A**	**C**	toluene	72	26	<1:92:8	83:17	4:1

4	**A**	**D**	toluene	40	26	6:76:20	82:18	5:1
5	**A**	**B**	**toluene**	**198**	**6**	**(17~12):83:<4**	**9:1**	**93:7**
6	**A**	**B**	DMSO	48	26	100:0:0	–	–
7	**A**	**B**	EtOAc	96	26	11:85:5	87:13	5:1
8	**A**	**B**	2-PrOH	84	26	3:93:7	80:20	4:1

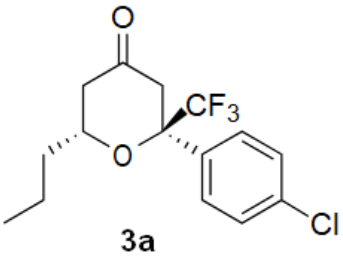
[a] Conditions: aryl trifluoromethyl ketone **2a** (3.0 mmol), enone **1a** (1.0 mmol), amine (0.2 mmol), andacid (0.4 mmol) in toluene (2.0 mL). The progress of the reaction was monitored and ^{1}H NMR analysis.The ratio **1**:**3a**:**4a** (in which **3a** = **3a-1** + **3a-2**) and the dr (**3a-1**:**3a-2**) were determined on before of the purification at the indicated time by ^{1}H NMR analysis. The er of purified **3a-1** are by the determined of HPLC analysis.

With the best conditions identified, reactions using different enones and aryl trifluoromethyl ketones are performed (Table 2). For the reactions of alkyl enones, product tetrahydropyranone derivatives **3** were obtained with diasteromer ratio (dr) 4:1 ~ 9:1 (**3a-h**). The major diastereomer of **3** was isolated as a single diastereomer in each of all the belongings shown in Table 2. The enantiomer ratio (er) values of the major diastereomers obtained from the reactions of alkyl enones were in a range of 93:7 ~ 90:10 (**3a-h**). The absolute configuration of the main diastereomer of **3a** (i.e., **3a-2**) was determined to be (*R*,*R*) as shown in the Table 2 by correlating with (*R*,*R*)-**3a-2** obtained from (*R*)-**4a**[6] by an acid-catalyzed oxa-Michaelcyclization[9] (Scheme 2).

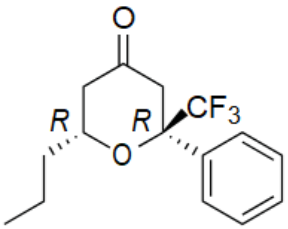
Table 2. Scope of the oxa-hetero-Diela-Alder reaction[a]



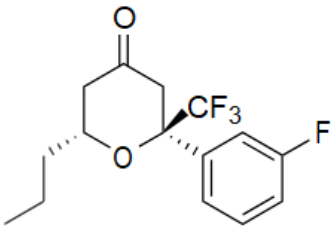
6^O C 8.6 days



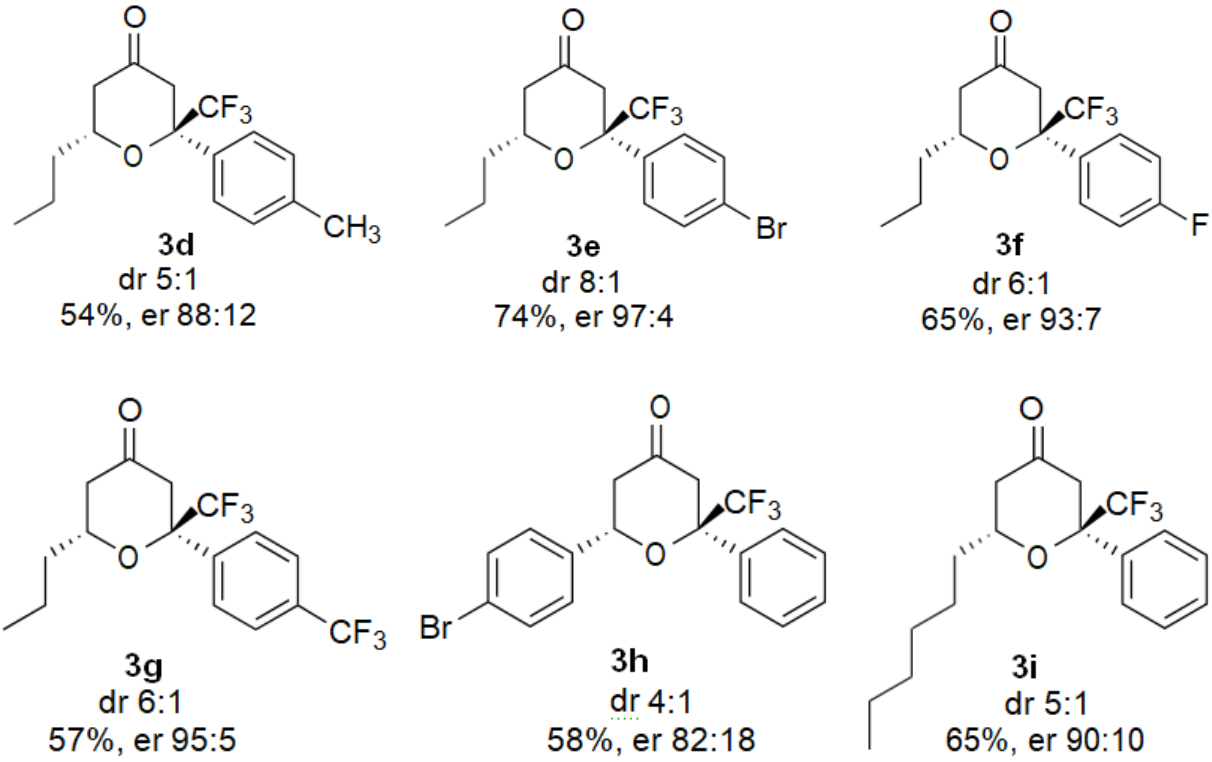
3a
dr 6:1
70%, er 96:4



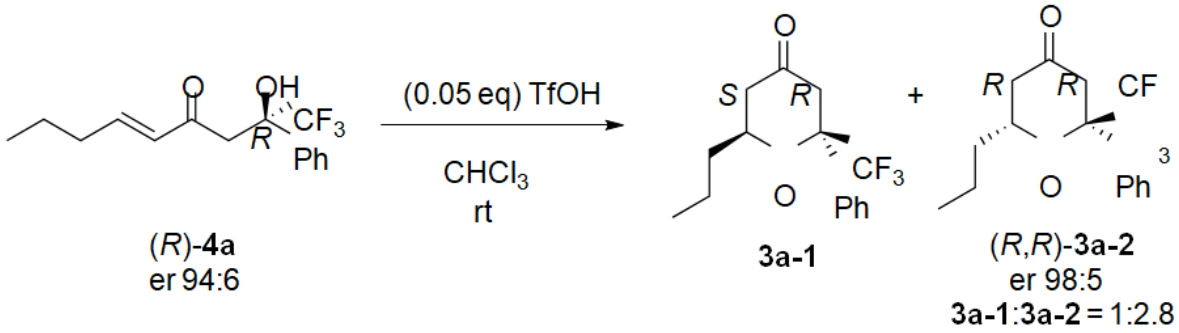
3b
dr 8:1
72%, er 92:8



3c
dr 7:1
60%, er 94:6



There are so many Conditions: aryl trifluoromethyl ketone **1** (3.0 mmol), enone **2** (1.0 mmol), acid **A** (0.4 mmol) in toluene (2.0 mL) and amine catalyst **B** (0.2 mmol),at 6°C for 8.6 days. The dr determined by ^{1}H NMR analysis on before the purification, the inaccessible yield of the main diastereomer of **3** as single diastereomer, and the er of the purified major diastereomer of **3** by HPLC analysis are shown.

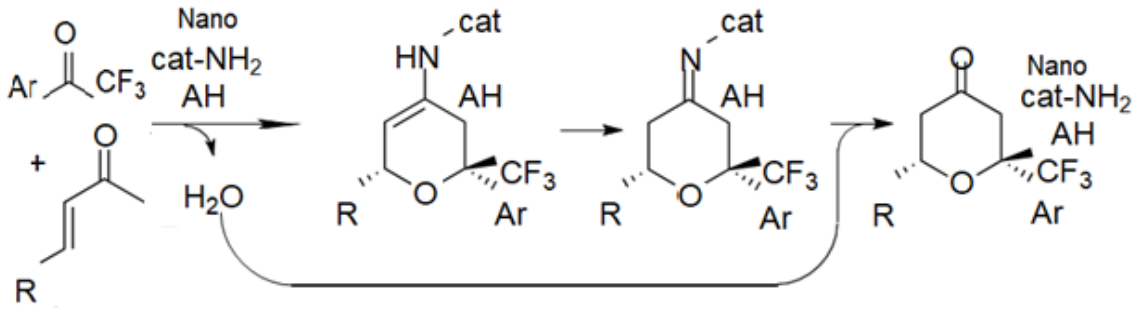


Method 2. A projected lane of the processes the enamine are formed by through the [4+2] cycloaddition from the enone with the amine *in situ* with the aryl trifluoromethyl ketone

In synopsis, enantioselective oxa-hetero-Diels-Alder reactions of enones, we have developed by aryl trifluoromethyl ketones that the derivatives of tetrahydropyranone are formed as the result. The main use of the system of nano catalyst described here, the tetrahydropyranone derivatives action of diastereomers that are the different structure those obtained in past reactions of oxa-hetero-Diels-Alder reactions of enones by the synthesized of aryl trifluoromethyl ketones with the enantioselectivities and high diastereo- and the singlediastereomers isolated processes as a outcome of the good yields.

Method 3. Renovation for the used in the determination of the stereochemistry of different compounds **3a and 3b to the** mechanism of the system of the nano catalyzed reactions by the nano catalyst composed of acid derivative **A** and amine derivative **B** , the structure of **3b** and the equivalent produce of aldol and the drand er values of **3b** were analyzed at different points of time. Aldol product was present in 5% (8 days) to 8% (3.5 days); In before of the formation of 3b, there are no accretion was observed at the present of Aaldol. From the reaction stage at the 80% conversion (at 8 days), and the stage at the 48% conversion (determined by ^{1}H NMR analysis as the yield of both diastereomers of **3b**; at 3.5 days) the dr of **3b** was basically the er of the foremost diastereomer of **3b** was 5:98 and the same value (dr 88:12 ~ 84:16). No important changes in the er and the dr values were identified during the processes of reaction. The recommend of results are that derivative of tetrahydropyranone **3b** is formed as kinetically in the core way of the nano catalyzed reaction by the acid **B** -amine **A of the system of nano** catalyst The foremost trail may be the [2+4] cycloaddition reaction of the enamine formed from the enone by the amine in situ and the ketone carbonyl

group[2a,b,3] are showed in the method 2 , even if the study of further is required to explain the detailed in the mechanism as follows



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