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COMMUNICATION

Mechanochemical milling promoted solvent-free imino Diels–Alder reaction catalyzed by FeCl₃: diastereoselective synthesis of *cis*-2, 4-diphenyl-1,2,3,4-tetrahydroquinolines

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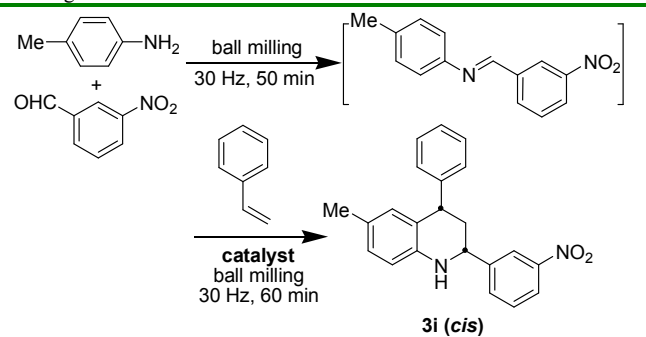
Under mechanochemical ball-milling at room temperature, FeCl₃ promoted Diels–Alder cycloaddition of styrene with *in situ* generated N-aryl aldimines in absence of any solvent afforded exclusively *cis*-2, 4-diphenyltetrahydroquinolines in good to excellent yields within 90 minutes. The isolation work up just involves washing the resulting reaction mixture with water and recrystallization from EtOH/H₂O. The advantages of high diastereoselectivity, short reaction time, free use of organic solvent, low cost, employment of cheap, easily available and nontoxic catalyst, and simple work-up procedure make this protocol a very efficient and green alternative to traditional methods for constructing these kinds heterocyclic skeletons.

Natural and synthetic tetrahydroquinolines (THQs) are of great importance in medicinal chemistry, and this kind of compounds have displayed various biological bioactivities.¹ Therefore, the development of efficient synthesis of THQs has been actively investigated. Indeed, a large number of methods have been reported for the construction of polysubstituted THQs.² Typically, the Povarov reaction, a [4+2] Diels–Alder reaction between N-arylimines and electron-rich dienophiles, is one of the most powerful and successful routes to rapidly construct this kind of privileged backbone.³ This imino Diels–Alder cycloaddition reactions can be promoted by many catalysts, such as various Lewis acids,^{3, 4} transition metal carbonyls,⁵ lanthanide triflates,⁶ trifluoroacetic acid,⁷ 2,3-dichloro-5,6-dicyano-pbenzoquinone (DDQ),⁸ triphenyl phosphonium perchlorate,⁹ etc. Frankly, most of these methods are efficient enough, but there are still some drawbacks such as rigorous or hazardous conditions, use of organic solvent, long reaction time, intractable side reactions or low selectivity, tedious isolation procedures and so on. To circumvent these problems, one of the best alternatives is to perform these reactions under solvent-free conditions. Among

current solvent-free techniques, mechanochemical milling has recently been contributing more and more for efficient promotion of various organic reactions in a greener way.^{10, 11} Keeping in mind the above facts and continuing our research on mechanochemical milling promoted reactions for synthesis of nitrogen-containing compounds,¹² we herein wish to report a FeCl₃-promoted solvent-free imino Diels–Alder reaction for diastereoselective synthesis of *cis*-2,4-diphenyl-1,2,3,4-tetrahydroquinolines.

Firstly, we chose the synthesis of *cis*-6-methyl-2-(3-nitrophenyl)-4-phenyl-1,2,3,4-tetrahydro-quinoline (**3i**) as the model reaction to screen an optimal catalyst (Table 1).

Table 1. Screening of optimal catalyst for synthesis of **3i** under ball milling^a



Entry	Catalyst	Yield (%) ^b
1	ZnCl ₂	76
2	AlCl ₃	85
3	CuCl ₂	15
4	FeCl ₃	86
5	Cu(OAc) ₂	10
6	Co(OAc) ₂	not detected
7	Mn(OAc) ₃	trace
8	Pd(OAc) ₂	trace
9	BF ₃ ·OEt ₂	81
10	Cu(OTf) ₂	56
11	TFA	48
12	<i>p</i> -TsOH	12
13	KHSO ₄	trace
14	KH ₂ PO ₄	not detected

^a Reactions were carried out with 4-methylaniline (2.0 mmol), 3-nitrobenzaldehyde (2.0 mmol), styrene (2.5 mmol) and catalyst (0.5 mmol) under ball milling at room temperature. ^b Determined by HPLC analysis based on 4-methylaniline.

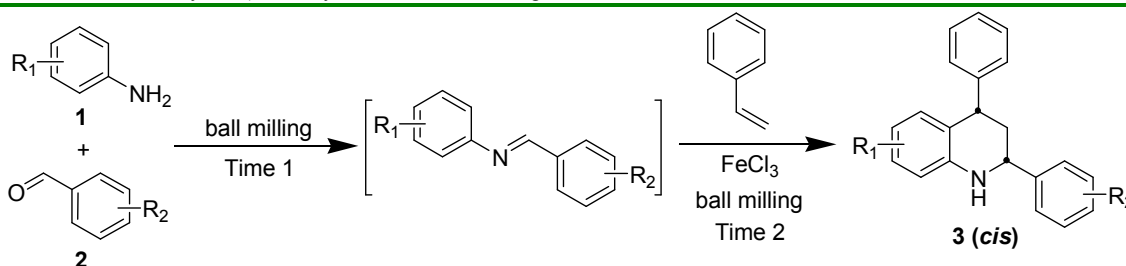
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†Electronic Supplementary Information (ESI) available: [experimental section, characterization details, NMR spectra for all products, and crystallographic data (CCDC993488, 993489) in CIF format.]. See DOI: 10.1039/b000000x/

A variety of Lewis acids and Brønsted acids were attempted, which have been extensively studied for traditional synthesis of tetrahydroquinolines in solution. The results were outlined in Table 1, which demonstrated that strong Lewis acids such as ZnCl₂, AlCl₃, FeCl₃ and BF₃·OEt₂ (entry 1, 2, 4, 9) promoted this Diels–Alder reaction to a great extent, while

Brønsted acids and other relatively weak Lewis acids worked too inefficient or cannot work at all. In contrast, FeCl₃ exhibits the best efficiency. Furthermore, considering its easy availability, low price, sustainability, non-toxicity, and environmentally friendly properties,¹³ we next selected FeCl₃ to clarify the generality of substrate scope.

Table 2. Diastereoselective synthesis of *cis*-2,4-diphenyl-1,2,3,4-tetrahydroquinolines via imino Diels–Alder reaction of *in situ* generated imine (from anilines **1** and benzaldehydes **2**) with styrene under ball milling^a



Entry	R ₁	R ₂	Product 3 ^b	Reaction time (min)		Yield (%) ^c
				Time 1	Time 2	
1	H	H	3a	90	90	71
2	H	4-Cl	3b	90	90	79
3	H	4-NO ₂	3c	75	90	75
4	H	3-NO ₂	3d	75	90	83
5	4-Me	H	3e	90	90	85
6	4-Me	4-Me	3f	75	90	80
7	4-Me	4-Cl	3g	60	90	82
8	4-Me	4-NO ₂	3h	50	90	83
9	4-Me	3-NO ₂	3i	50	90	74
10	4-OMe	H	3j	50	90	80
11	4-OMe	4-Me	3k	40	90	81
12	4-OMe	4-Cl	3l	30	90	77
13	4-OMe	4-NO ₂	3m	30	90	70
14	4-OMe	3-NO ₂	3n	30	90	73
15	4-Cl	4-Cl	3o	60	90	91
16	4-Cl	4-NO ₂	3p	50	90	83
17	4-Cl	3-NO ₂	3q	50	90	82
18	3-Cl	4-NO ₂	3r	50	90	87
19	3-Cl	3-NO ₂	3s	50	90	86

^a Reactions were carried out with aniline **1** (2.0 mmol), benzaldehyde **2** (2.0 mmol), and afterward added styrene (2.5 mmol) and FeCl₃ (0.5 mmol) under ball milling (vibration frequency: 30 Hz) at room temperature. ^b Characterized by mp, IR, ¹H NMR, ¹³C NMR and HRMS analysis. ^c Isolated yield combined from two parallel runs by washing the resulting reaction mixture with water and recrystallization in EtOH/H₂O.

As shown in Table 2, a series of substituted anilines and benzaldehydes were examined. To our delight, the reactions worked well with substituted anilines and benzaldehydes bearing either electron-donating or electron-withdrawing groups on the benzene ring. In contrast, similar reactions with anilines bearing electron-donating substituents exhibited relatively lower reactivity when performed in organic solvents. Furthermore, all the desired products **3a–s** with high structural diversity were obtained in good to excellent isolated yield through a simple work up, just including washing the resulting reaction mixture with water and recrystallization in EtOH/H₂O. Under herein ball milling at room temperature, these cycloaddition reactions can be almost completely accomplished within 90 minutes, which were obviously faster than most conventional solution cases. The rapid conversion under this high speed vibration milling condition is probably caused by the high mechanical energy from local high

pressure, friction, shear strain and so on.¹⁴

It is worthy to point out that herein solvent-free ball milling promoted reactions afforded the corresponding THQs **3** exclusively in *cis*-(2e, 4e) configuration based on HPLC analysis of the resulted reaction mixtures. The high diastereoselectivity may be ascribed to high local concentration of the reactants under this mechanochemical and solvent-free condition, which may result in an enhanced second-order reaction rate and thus prefer to selective formation of products via kinetic control.¹⁵ There is a fact that when the reaction for synthesis of tetrahydroquinolines **3i** was performed by refluxing in organic solvents such as CH₂Cl₂ and THF, minor *trans*-diastereomer was detected. The *cis*-(2e, 4e) configuration is indicated by the diagnostic coupling constants of the relevant protons on the saturated THQ ring from ¹H NMR analysis. That is, the large vicinal coupling constants $J_{2a, 3a}$ and $J_{3a, 4a} = 9.9\text{--}12.0$ Hz for this form indicate

an axial–axial relationship, and the aryl groups on C-2 and C-4 are both pseudoequatorial and thus located in *cis*-configuration.¹⁶ In addition, this stereochemistry was further unambiguously confirmed by single-crystal X-ray diffraction

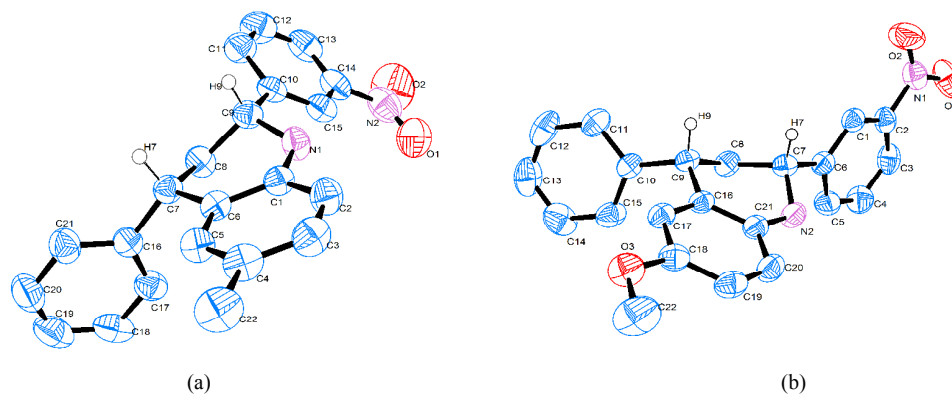


Figure 1. Single-crystal X-ray structure of compound **3i** (a) and **3n** (b).

In summary, under mechanochemical ball-milling at room temperature, the FeCl₃ promoted Diels-Alder cycloaddition reactions of styrene with *in situ* generated N-aryl aldimines in absence of any solvent afforded exclusively *cis*-2, 4-diphenyltetrahydroquinolines in good to excellent yields within 90 minutes. The isolation work up just involves washing the resulting reaction mixture with water and recrystallization in EtOH/H₂O. This novel protocol exhibits the advantages of high diastereoselectivity, short reaction time, free use of organic solvent, low cost, employment of cheap, easily available and nontoxic catalyst, and simple work-up procedure. These merits make this protocol a very efficient and green alternative to traditional methods for synthesis of these kinds of compounds, and even can presumably be extended to the construction of other heterocyclic skeletons.

We are grateful to financial support from National Natural Science Foundation of China (21242013).

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analysis of two selected examples **3i** and **3n** (Figure 1), showing that the substituents in the saturated part of the tetrahydroquinoline occupy the equatorial positions, strongly confirming that the reaction was highly diastereoselective.¹⁷

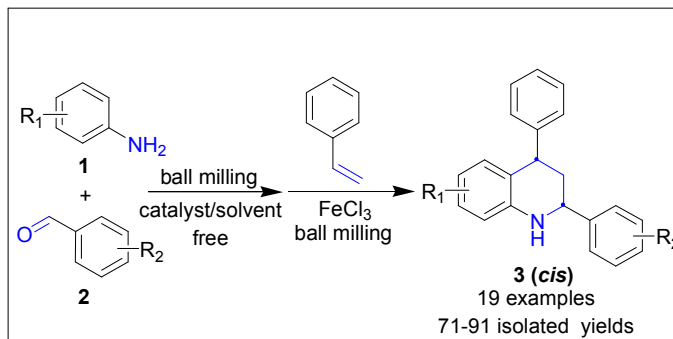
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17 CCDC-993488 (**3i**) and 993489 (**3n**) containing the supplementary crystallographic data can be obtained free of charge from Cambridge

Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table of contents entry

Colour graphic:



Text:

Cis-2,4-diphenyl-1,2,3,4-tetrahydroquinolines were diastereoselectively synthesized by FeCl_3 -promoted solvent-free Diels-Alder reaction of in situ generated imine with styrene under ball milling.