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Organocatalytic Hantzsch Type Reaction Using Aryl Hydrazines, Propiolic Acid Esters and Enals: Enantioselective Synthesis of Paroxetine

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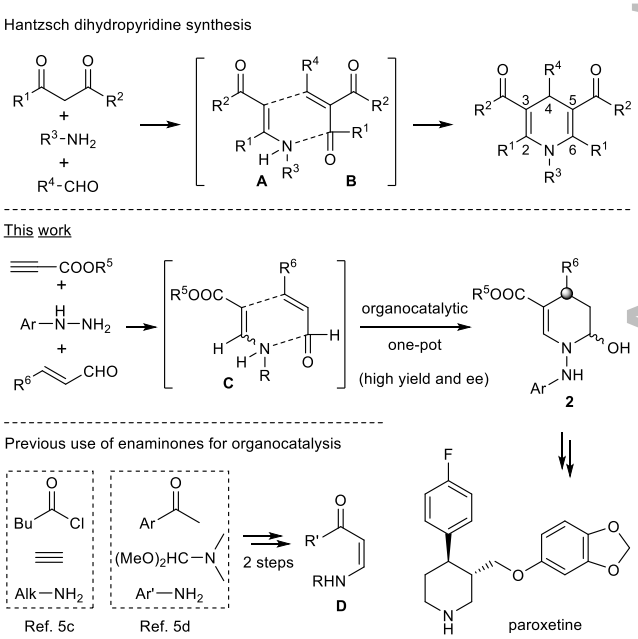
Abstract. Aryl hydrazines, propiolic acid esters and enals serve as a viable substrate combination for an organocatalytic enantioselective Hantzsch type reaction. The method converts readily available starting materials into important chiral heterocycles with good to excellent yields and enantioselectivities, and has addressed the longstanding scope limitation of the classic Hantzsch reaction in the asymmetric synthesis of 2,6-unsubstituted hydropyridines. The synthetic utility has been demonstrated by the concise enantioselective synthesis of paroxetine.

Keywords: Organocatalysis; Hantzsch; Hydropyridine; Paroxetine; Enhydrazine

The Hantzsch dihydropyridine synthesis, first reported in 1880s,[1a,1b] refers to the one-pot condensation of β-keto esters or 1,3-dicarbonyl compounds with aldehydes and ammonia/amines, involving enamines **A** and α,β-unsaturated carbonyls **B** as the reactive species, to afford 1,4-dihydropyridines (Scheme 1).[1c] Since the discovery, the Hantzsch type synthesis, either the original multicomponent protocol or modifications using pre-formed enamines or α,β-unsaturated carbonyls, has become a powerful strategy for the rapid synthesis of hydropyridines, pyridines (upon oxidation) and piperidines (upon reduction), which are the core structures of a diverse range of biologically important molecules.[2] Significant progresses in the catalytic enantioselective Hantzsch synthesis have also been achieved recently, which have further improved the synthetic utility of this traditional reaction.[3,4] Despite of the notable achievements in this area, the asymmetric synthesis of 2,6-unsubstituted hydropyridines has been challenging mechanistically due to the difficulties in using β-formyl carbonyls/esters (Scheme 1, R^1 = H) as the substrates for asymmetric catalysis. In this context, organocatalytic reactions of pre-formed enamines (**A**: R^1 = H, Scheme 1) with enals represent an appealing approach to address the above mentioned problem.[5] Among the scattered known examples, high enantioselectivities have been elegantly achieved by the groups of Kanger[5c] and Enders[5d] using pre-formed enaminones **D** (Scheme 1), however, the preparations of such substrates are not straightforward, which have limited the overall synthetic efficiency and utility. Thus, it is highly desirable to develop other viable substrates particularly for the one-pot asymmetric Hantzsch type synthesis to generally address this scope limitation.



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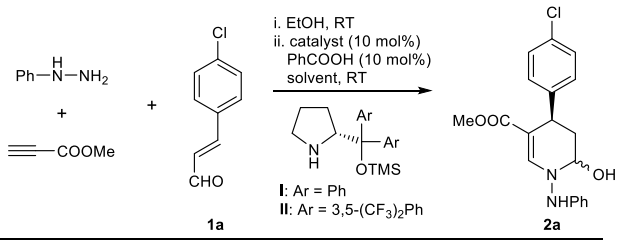
Scheme 1. The organocatalytic enantioselective Hantzsch type reactions.

Our interest in the Hantzsch reaction was partially inspired by the structure of paroxetine, a blockbuster serotonin inhibitor for the treatment of depression and anxiety related disorders.[6] We envisioned that the Hantzsch product, generated by the condensation of an enamino ester **C** and an enal, could serve as a viable intermediate for the efficient preparation of this therapeutic agent (Scheme 1). While many creative methods have been developed in the context of asymmetric synthesis of paroxetine,[7,8] the Hantzsch reaction, though straightforward from a retrosynthetic view, has not been used before presumably due to the difficulties of handling enamino esters **C** as the substrates for asymmetric catalysis. Using propiolic acid esters as surrogates of β-formyl esters represents an appealing and practical way for the generation of such enamino esters via simple conjugate addition with amines.[9] In 2010, the group of Takemoto reported a single substrate, generated by the addition of 4-methoxyl aniline to ethyl propiolate, for the bifunctional thiourea catalyzed Hantzsch reaction with enals.[5a,5b] Though conceptually feasible, the stepwise process suffers from low yielding in the substrate synthesis and moderate enantioselectivities in the Hantzsch reaction. The application of such enamino esters in a secondary-amine catalyzed process would be more challenging, as even a small amount release of the amines from the enamino esters (by reversible process or hydrolysis) would compete with the catalyst. Inspired by the relatively higher stability of the corresponding enhydrazines (Scheme 1, **C**: R = NHAr)[10] and the recent utilizations of hydrazones[11] in the Hantzsch reaction, we surmised that readily available aryl hydrazines, propiolic acid esters and enals could serve as a new substrate combination for the one-pot Hantzsch type synthesis. Specifically, the telescoped process involving the generation of the enhydrazines **C** by the addition of aryl hydrazines to propiolic acid esters and their subsequent annulation with enals under organocatalysis would enable the efficient asymmetric synthesis of tetrahydropyridines **2**.[12] Of note, the easy of the cleavage of the N-N bond for deprotection is another advantage of using aryl hydrazines in the Hantzsch reaction. Herein, we report the realization of a secondary-amine catalyzed one-pot Hantzsch type synthesis employing aryl hydrazines, propiolic acid esters and enals with good to excellent yields and enantioselectivities, and demonstrate the synthetic utility of the method by the concise asymmetric synthesis of the anti-depressive drug paroxetine.

Table 1. Optimization of the reaction conditions.[a]



entry	catalyst	solvent	yield[b]	ee[c]	dr[d]
1	I	EtOH	79	97	3.0:1
2	I	DCM	77	98	3.0:1
3	I	DCE	73	97	2.5:1
4	I	EtOAc	78	99	2.5:1
5	I	Toluene	81	99	2.5:1
6	I	CH_3CN	96	98	4.0:1
7[e]	I	CH_3CN	76	99	6.5:1
8[f]	I	CH_3CN	65	97	4.0:1
9[g]	I	CH_3CN	70	97	4.0:1
10	II	CH_3CN	56	45	4.0:1

[a] Phenyl hydrazine (0.1 mmol) and methyl propiolate (0.1 mmol) was stirred in EtOH (0.3 mL) at RT for 3 h; EtOH was removed by concentration, and the specified solvent (0.3 mL) was added to the same vial followed by the addition of **1a** (0.12 mmol), the additive (10 mol%) and the catalyst (10 mol%). The reaction was stirred at RT for 24 h. [b] Isolated yield. [c] Determined by Chiral HPLC analysis. [d] Determined by ^{1}H NMR. [e] Without benzoic acid. [f] Using 5 mol% catalyst I. [g] Using acetonitrile as the sole solvent for the enhydrazine generation and subsequent annulation.

A model reaction of phenyl hydrazine, methyl propiolate and 4-chlorocinnamaldehyde **1a** was carried out first to test the feasibility of our hypothesis (Table 1). Diphenylprolinol TMS ether **I**[13] was selected as the first organocatalyst for the reaction due to its commercial availability and widely usage in the activation of enals via iminium ion.[14] We initially tested the reaction using ethanol as the sole solvent. Phenyl hydrazine and methyl propiolate were allowed to react at room temperature first, upon completion of the generation of the enhydrazine (by TLC), enal **1a**, the organocatalyst **I** (10 mol%) and benzoic acid (10 mol%) were added to the same vial for the subsequent annulation. By such a one-pot protocol, **2a** was obtained in 79% yield and 97% ee (Table 1, entry 1).[15] The OH-containing stereogenic center consisted of a pair of diastereomers, with anti / syn = 3:1. The results were very promising with satisfactory enantioselectivity, but the yield was not optimal. Then we tried the model reaction using different solvents. As the enhydrazine generation was best performed in ethanol, an operation involving concentration and solvent switch was added to the above one-pot protocol (see foot [a] in Table 1). Among of the various solvents tested, acetonitrile afforded the best results with excellent enantioselectivity and nearly quantitative yield (entry 6). As the OH-containing stereogenic center is epimerizable and inconsequential for the synthesis of paroxetine, we did not go further to optimize the

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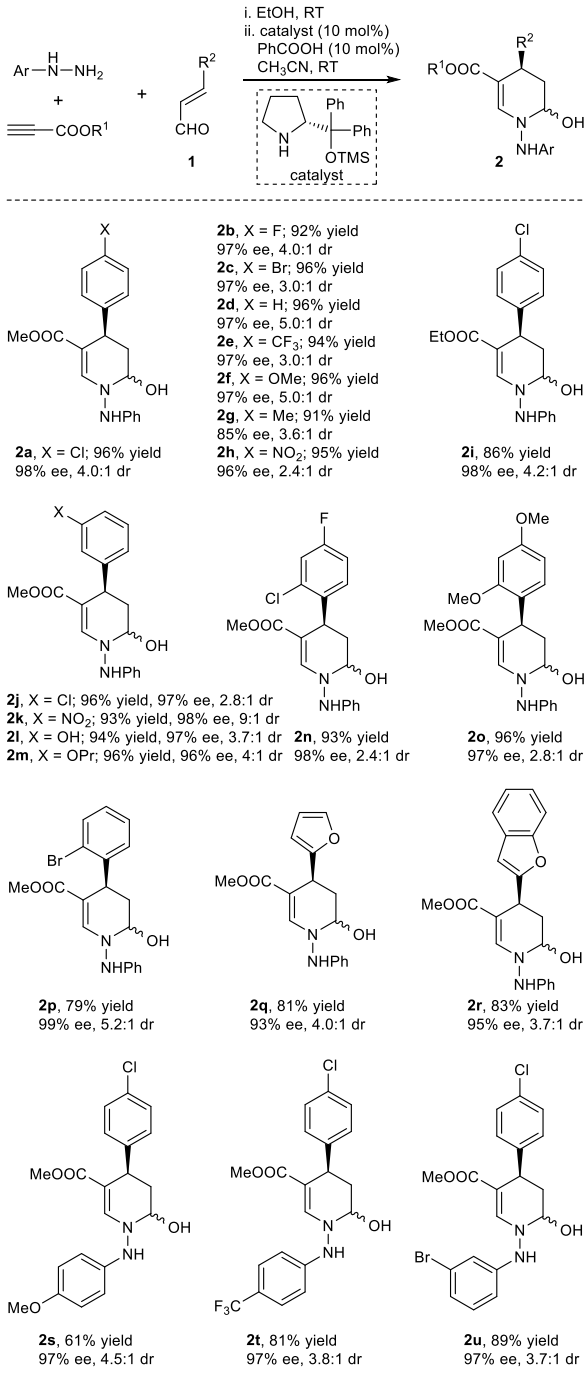
diastereomer ratio. It should be noted that much lower reaction yields were observed when benzoic acid was not used as an acidic additive, or 5 mol% catalyst **I** was used, or acetonitrile was used as the sole solvent for both the enhydrazine generation and subsequent annulation (entry 7-9). The switch of catalyst to **II** gave only moderate yield and ee (entry 10). The structure of **2a** and its absolute configuration were determined by single-crystal X-ray diffraction.[16]



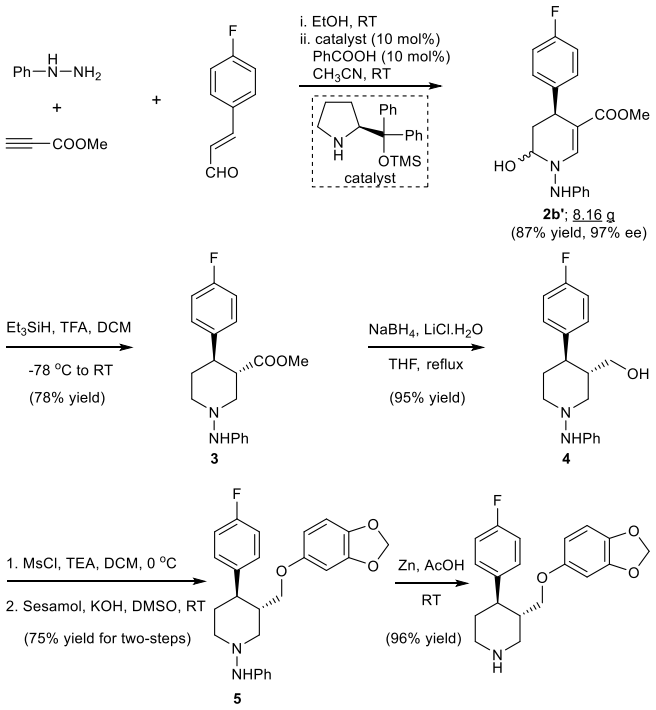
Scheme 2. Substrate scope of the organocatalytic one-pot Hantzsch type reaction.

With the optimized reaction conditions identified, the substrate scope of the organocatalytic Hantzsch type reaction was next examined (Scheme 2). A variety of aromatic α,β-unsaturated aldehydes proved to be efficient substrates, generating tetrahydropyridines **2** with good to excellent yields and enantioselectivities. When the R^2 groups were substituted benzenes, the reactions tolerated both the electronic and steric properties of the substituents (**2a-2p**). A series of functional groups, such as halogens, nitro and hydroxy, could be thus introduced into the products, which could serve as handles for further elaboration. Besides methyl propiolate, ethyl propiolate could also be suitable substrate for the Hantzsch type reaction with similar results (**2i**). Furthermore, the substrate scope of the reaction could include heterocyclic α,β-unsaturated aldehydes. Thus, the enantioselective Hantzsch type reactions could successfully allow for the incorporation of heterocycles, such as furan and benzofuran, into the products with good to excellent yields and ees (**2q-r**). The structures of aryl hydrazines could also be varied, tolerating both electron donating and withdrawing groups at varied positions (**2s-u**). Of note, the less reactive aliphatic α,β-unsaturated aldehydes could not be used as substrates for the reactions.

Finally, to demonstrate the synthetic utility of the one-pot organocatalytic Hantzsch type reaction, we turned to the asymmetric synthesis of the anti-depressive drug paroxetine. The structure of this therapeutic agent has stimulated many creative method developments for its synthesis.[8] Among them, two organocatalytic approaches have been reviewed by Howell to be potentially practical.[17] The group of Jørgensen has pioneered the use of an organocatalytic Michael addition of malonate with 4-fluorocinnamaldehyde followed by reductive amination–lactamization to afford the lactam intermediate for paroxetine synthesis.[8b] The group of Vesely / Moyano / Rios[8h-i] has further streamlined the synthesis by using amidomalonates directly, however, this method requires the use of trifluoroethanol as the solvent, limiting its utility in scale-up activities.[15] The group of Ma[8f] and Most recently, the group of Otvos / Kappe[8v] have elegantly made significant improvements of Jørgensen's approach by using water as a green solvent and continuous flow synthesis. Though such Michael-addition based approaches are very efficient and concise, the use of lactams as intermediates requires the handle of strong reducing agents, such as LAH (lithium aluminium hydride) and BH_3, generating concerns about safety and operational simplicity, particularly in scale-up activities.

The gram-scale organocatalytic Hantzsch reaction of phenyl hydrazine, methyl propiolate and 4-fluorocinnamaldehyde was carried out first using the (*S*)-diphenylprolinol TMS ether catalyst (Scheme 3). The reaction successfully afforded the key intermediate **2b'** (8.16 g) in 87% yield and 97% ee.[18] Of note, this one-pot reaction employed all commercially available starting materials, catalyst

and industrially friendly solvents, and proceeded at room temperature. Subsequent diastereoselective reduction of the hydropyridin-2-ol moiety was achieved by the treatment with triethylsilane, a cheap and mild reductant.[19] The reduction of the ester group was realized using simple $NaBH_4$, furnishing alcohol **4** in 95% yield. The installation of the sesamol side chain was then achieved by a two-step sequence, involving mesylate activation and SN_2 alkylation. Finally, reductive cleavage of the N-N bond by zinc powder produced paroxetine in 96% yield. Our asymmetric synthesis of paroxetine took only six steps and featured the use of all readily available starting materials, the use of asymmetric catalysis to set up the stereogenic centers, the use of mild and simple reagents for reduction and late stage deprotection (via N-N bond cleavage). We believe that the simplicity and efficiency of our synthesis should be well suited for further scale-up activities.



Scheme 3. Enantioselective synthesis of paroxetine.

In summary, we have developed an organocatalytic enantioselective Hantzsch type reaction using aryl hydrazines, propiolic acid esters and enals to afford hydropyrines with excellent enantioselectivities. The method serves as a general approach to address the longstanding scope limitation of the Hantzsch reaction in the asymmetric synthesis of 2,6-unsubstituted hydropyridines. The synthetic utility of the method has been demonstrated by the concise asymmetric synthesis of paroxetine.

Experimental Section

Phenyl hydrazine (10.8 mg, 0.1 mmol) and methyl propiolate (8.4 mg, 0.1 mmol) was stirred in EtOH (0.3 mL) at RT for 3 h; EtOH was removed by concentration, and CH_3CN (0.3 mL) was added to the same vial followed by the addition of 4-fluorocinnamaldehyde (18 mg, 0.12 mmol), benzoic acid (1.2 mg, 0.01 mmol) and the catalyst (3.3 mg, 0.01 mmol). The reaction was stirred at RT for 24 h. The mixture was concentrated under reduced pressure and purified by via silica gel column chromatography (eluting with petroleum ether/EtOAc = 15:1 to 5:1) to afford the desired product **2b** as a mixture of two diastereomers (92% combined yield, 97% ee, dr: anti/syn = 4:1).

Acknowledgements

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[15] The yield of **2a** referred to the mixture of the two diastereomers. The ee of **2a** was obtained by the HPLC analysis of the major (anti) isomer. As a representative example, full characterization of both the anti and syn diastereomers of **2b**, including ^{1}H NMR, ^{13}C NMR and chiral HPLC spectra, can be found in the supporting information, indicating that the ees of both the diastereomers were identical.

[16] CCDC 2008770 (the anti-isomer of **2a**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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[18] For the post-functionalization of 2b' to dihydropyridone and 1,4-dihydropyridine, see supporting information.

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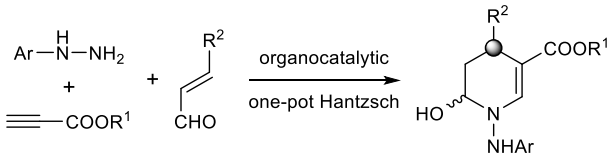

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