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$Sc(OTf)_3$-Catalyzed Three-Component Cyclization of Arylamines, β,γ-Unsaturated α-Ketoesters, and 1,3-Dicarbonyl Compounds for the Synthesis of Highly Substituted 1,4-Dihydropyridines and Tetrahydropyridines

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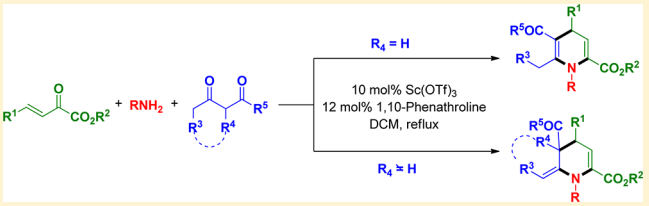
Supporting Information

ABSTRACT: A $Sc(OTf)_3$-catalyzed three-component cyclization reaction of arylamines, β,γ-unsaturated α-ketoesters and 1,3-dicarbonyl compounds was developed to synthesize highly substituted 1,4-dihydropyridines and fused bicyclic tetrahydropyridines carrying a quaternary all-carbon center.



Multicomponent reactions (MCRs) represent one of the most efficient and atom-economic means to build up structural complexity and diversity.[1] The development of new MCRs has remained an intense research interest in the organic community. 1,3-Dicarbonyl compounds and their derivatives can be easily tuned to serve as a nucleophile and/or an electrophile. This feature along with their inherently densely installed functional groups make them an important class of versatile and efficient synthetic platforms in organic transformations. In recent years, the utilization of 1,3-dicarbonyl compounds in MCRs has become more prevalent.[2]

Six-membered nitrogen-containing heterocyclic compounds, such as dihydropyridines (DHPs) and tetrahydropyridines (THPs), have been recognized as a class of highly important molecular skeletons abundant in natural products, pharmaceuticals, agrochemicals, and functional materials[3] and as key intermediates in the preparation of nitrogen-containing alkaloids.[4] Much effort has been devoted to the development of new methodologies to access dihydropyridines (DHPs) and tetrahydropyridines (THPs).[5] Among a number of methodologies developed to date, the Hantzsch reaction utilizing an amine, an aldehyde, and two 1,3-dicarbonyl compounds is a concise and conventional approach to synthesize symmetrical 1,4-DHPs.[6] Unsymmetrical 1,4-DHPs provide much larger structural diversity, and are thus of a more biological and synthetic interest. Although the synthesis of unsymmetrical 1,4-DHPs has been achieved through the Hantzsch-like reactions by using two different 1,3-dicarbonyl compounds, these reactions suffer from side reactions forming symmetrical 1,4-DHPs and are of limited substrate scope.[7] The development of new methodologies to access unsymmetrical 1,4-DHPs has attracted much attention in recent years.[8,9] The multicomponent cyclization reaction employing a 1,3-dicarbonyl compound, a α,β-unsaturated aldehyde, and an arylamine has appeared to be an efficient method to access unsymmetrical 1,4-DHPs,[9] making an ideal complement to the Hantzsch reaction (Scheme 1). However, this method is limited to α,β-unsaturated aldehydes, i.e., cinnamaldehyde. To our knowledge, enones have not been utilized in this reaction. This is likely due to the general understanding of lower activity of enones resulted from both electronic and steric factors. In our recent effort to develop an asymmetric aza-Diels–Alder reaction of cyclic ketones with unsaturated α-ketoesters and arylamines,[10] we found that, although the use of enone to form 1-azadiene is often coupled with slower rates of ketiminations resulting in extensive side reactions,[11] the aza-Diels–Alder reaction of an in situ formed 1-azadiene intermediate and a cyclic ketone is efficient enough to dominate through the enamine–metal Lewis acid cooperative catalysis, leading to the formation of aza-Diels–Alder products in high yields. We envision a similar cyclization reaction of β-ketoesters using metal Lewis acid catalysis. Due to the ease of formation of both an enol and an enamine intermediate from a β-ketoester, we speculate that this reaction can occur either through an enol and/or enamine pathway (Scheme 1). Herein, we report a $Sc(OTf)_3$-catalyzed three-component cyclization of arylamines, β,γ-unsaturated α-ketoesters and 1,3-dicarbonyl compounds to afford highly substituted unsymmetrical 1,4-DHPs and fused bicyclic tetrahydropyridines bearing a quaternary all-carbon center.

We initiated our investigation by examining the cyclization of 1,3-dicarbonyl compounds **1a**, β,γ-unsaturated α-ketoesters **2a** and *p*-methoxyaniline **3a** in the presence of 10 mol % of $Y(OTf)_3$ and $Cu(OTf)_2$ in THF at room temperature (Table 1, entries 1 and 2). The desired cyclization product **4a** was isolated in 33% yield from the reaction catalyzed by $Y(OTf)_3$. When DCM was used as the solvent, the NMR yield of this reaction increased to 45%. To further improve the yield, a

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Scheme 1

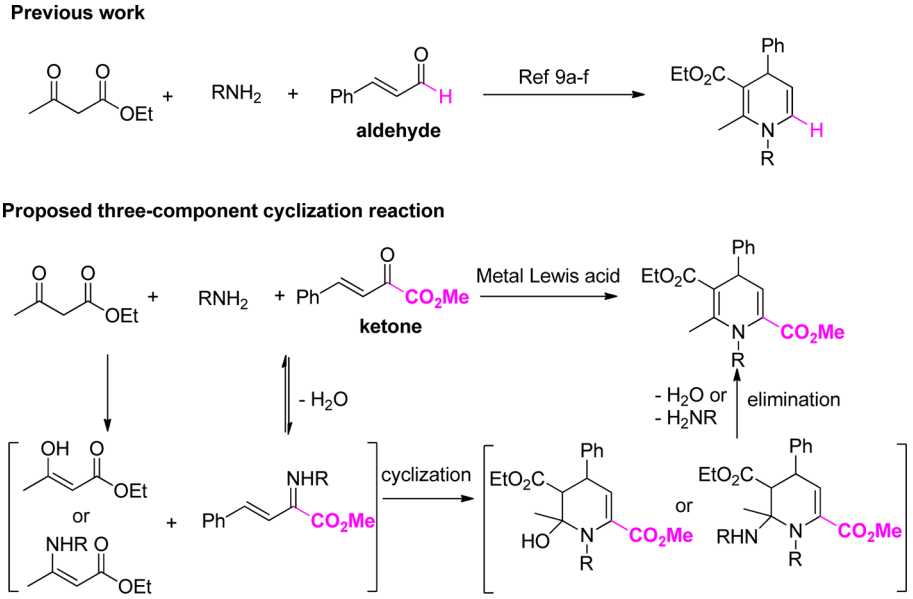
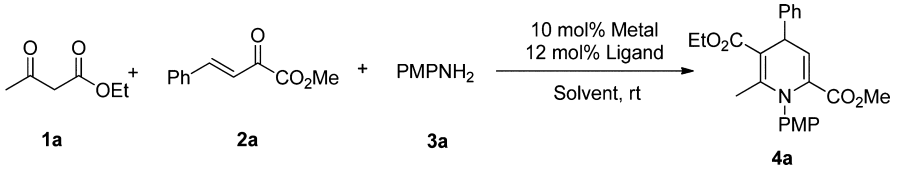


Table 1. Condition Screening



entry[a]	metal	ligand	solvent	time (h)	yield[b] (%)
1	$Y(OTf)_3$		THF	36	38 (33)
2	$Cu(OTf)_2$		THF	48	trace
3	$Y(OTf)_3$		DCM	36	45
4	$Zn(OTf)_2$		DCM	36	35
5	$Ni(ClO_4)_2{\cdot}6H_2O$		DCM	36	19
6	$Yb(OTf)_3$		DCM	36	33
7	$La(OTf)_3$		DCM	36	37
8	$Sc(OTf)_3$		DCM	36	57
9	$Sc(OTf)_3$		DCM	48	61
10	$Sc(OTf)_3$		MeOH	48	45
11	$Sc(OTf)_3$		DCE	48	48
12	$Sc(OTf)_3$		toluene	48	45
13	$Sc(OTf)_3$		CH_3CN	48	21
14	$Sc(OTf)_3$		THF	48	33
15	$Sc(OTf)_3$		CH_3Cl	48	60
16	$Sc(OTf)_3$	pyridine	DCM	48	65
17	$Sc(OTf)_3$	4,4-methyl-2,2-bipyridne	DCM	48	65
18	$Sc(OTf)_3$	1,10-phenanthroline	DCM	48	73
19[c]	$Sc(OTf)_3$	1,10-phenanthroline	DCM	18	91
20[c,d]	$Sc(OTf)_3$	1,10-phenanthroline	DCM	18	99 (92)

[a]Unless noted, reactions were carried out with 0.4 mmol of **1a**, 0.24 mmol of **2a**, 0.2 mmol of **3a**, and 10 mol % of catalyst in 2 mL of solvent. [b]NMR yield. The numbers in parentheses are isolated yields. [c]Under reflux. [d]The reaction was carried out under argon. PMP = 4-methoxyphenyl.

representative selection of Lewis acids including $Zn(OTf)_2$, $Ni(ClO_4)_2{\cdot}6H_2O$, $Yb(OTf)_3$, $La(OTf)_3$, and $Sc(OTf)_3$ were tested in DCM (Table 1, entries 3–8). $Sc(OTf)_3$ showed the best activity for this cyclization reaction. Prolonged reaction time only slightly increased the yield (Table 1, entry 9). Other solvents, such as methanol, toluene, acetonitrile and 1,2-dichloroethane (DCE) did not improve the yield (Table 1, entries 10–15). During the investigation, we found that addition of some pyridine-based ligands helped improve the yield of the reaction (Table 1, entries 9, 16–18). This is likely because of that the addition of these ligands helps enhance the stability of possible metal complex intermediates. Optimal conditions were obtained when 10 mol % of $Sc(OTf)_3$ and 12 mol % of 1,10-phenanthroline were used in DCM under argon at reflux, affording **4a** in 92% isolated yield (Table 1, entry 20).

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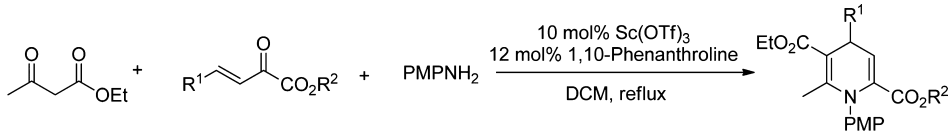
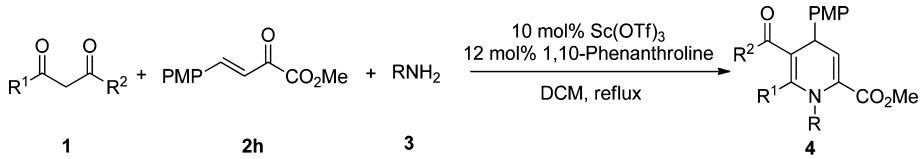
Table 2. Scope of β,γ-Unsaturated α-Ketoesters



entry[a]	2	R^1	R^2	4	time (h)	yield[b] (%)
1	**2b**	C_6H_5	$CH_2C_6H_5$	**4b**	20	90
2	**2c**	C_6H_5	$CH_2(4\text{-}NO_2C_6H_4)$	**4c**	14	90
3	**2d**	$4\text{-}MeC_6H_4$	Me	**4d**	21	79
4	**2e**	$4\text{-}ClC_6H_4$	$CH_2C_6H_5$	**4e**	18	87
5	**2f**	$4\text{-}BrC_6H_4$	Me	**4f**	20	83
6	**2g**	$4\text{-}BrC_6H_4$	$CH_2C_6H_5$	**4g**	22	93
7	**2h**	$4\text{-}MeOC_6H_4$	Me	**4h**	18	92
8	**2i**	$2,6\text{-}Cl_2C_6H_3$	Me	**4i**	23	94
9	**2j**	$C_6H_5CH{=}CH$	Et	**4j**	24	76

[a]Under argon, reactions were carried out with 0.4 mmol of **1a**, 0.24 mmol of **2**, 0.2 mmol of **3a**, 10 mol % of $Sc(OTf)_3$ and 12 mol % of 1,10-phenanthroline in 2 mL of DCM. [b]Yield of the isolated product. PMP = 4-methoxyphenyl.

Table 3. Scope of Arylamines and 1,3-Dicarbonyl Compounds



entry[a]	$1/R^1/R^2$	3	R	4	time (h)	yield[b] (%)
1	**1a**/Me/OEt	**3b**	C_6H_5	**4k**	36	83
2	**1a**	**3c**	$4\text{-}ClC_6H_4$	**4l**	72	80
3	**1a**	**3d**	$4\text{-}BrC_6H_4$	**4m**	48	74
4	**1a**	**3e**	$3\text{-}ClC_6H_4$	**4n**	24	63
5	**1a**	**3f**	$2\text{-}ClC_6H_4$	**4o**	24	85 (51:49)
6	**1a**	**3g**	$2\text{-}IC_6H_4$	**4p**	40	83 (54:46)
7	**1a**	**3h**	$3,4\text{-}(CH_3O)_2C_6H_3$	**4q**	24	65
8	**1b**/Me/OMe	**3a**	$4\text{-}MeOC_6H_4$	**4r**	20	88
9	**1c**/Me/O*t*-Bu	**3a**	$4\text{-}MeOC_6H_4$	**4s**	20	95
10	**1d**/Me/Me	**3a**	$4\text{-}MeOC_6H_4$	**4t**	48	78
11	**1e**/Ph/OEt	**3a**	$4\text{-}MeOC_6H_4$	**4u**	72	74

[a]Under argon, reactions were carried out with 0.4 mmol of **1**, 0.24 mmol of **2h**, 0.2 mmol of **3**, 10 mol % of $Sc(OTf)_3$, and 12 mol % of 1,10-phenanthroline in 2 mL of DCM. [b]Yield of the isolated product; the numbers in parentheses are the ratios of the two isomers. PMP = 4-methoxyphenyl.

Having obtained the optimized reaction conditions, we next investigated the scope of this three-component cyclization reaction of β,γ-unsaturated α-ketoesters **2** with 1,3-dicarbonyl compound **1a** and amine **3a**. The results are summarized in Table 2. Both electronic and steric factors of the substituents on the aromatic ring of enones **2** had no obvious effects on the yields of the reaction (entries 1−8). Introduction of an alkenyl substituent at the γ-position of the β,γ-unsaturated α-ketoester (**2j**) was well tolerated, affording the corresponding regioselective cycloadduct **4j** in 76% yields (entry 9).

We also investigated the scopes of the 1,3-dicarbonyl compounds (**1**) and the arylamines (**3**) for this transformation (Table 3). In general, the reaction of an arylamine with an electron-donating group at the *para*-position was faster than an arylamine having an electron-withdrawing group at the *para*-position (entries 1−7); the reactions of more sterically hindered ortho-substituted anilines also proceeded smoothly to give the desired 1,4-DHPs in high yields (entries 5 and 6). It is interesting to note that when an ortho-substituted aniline was used, extra axial chirality was created in the resulting 1,4-DHP (**4o** and **4p**) due to the restricted rotation of the neighboring groups (R^1, R, and CO_2Me). This structural feature can only be made possible when enones are used in the cyclization reaction. Both β-ketoesters and β-diketones turned out to be suitable substrates for this cyclization reaction (entries 8−11).

We also investigated the cyclization reaction of 2-substituted 1,3-dicarbonyl compounds with enone **2** and arylamines. The cyclization reaction of 2-substituted 1,3-dicarbonyl compounds would create a new all-carbon quaternary center, which is much more challenging to synthesize. We chose methyl 2-oxocyclohexanecarboxylate **1f** and methyl 2-oxocyclopentanecarboxylate **1g**. Compounds **1f** and **1g** would lead to the formation of bicyclic fused ring systems. As it turned out, both six-membered **1f** and five-membered **1g** reacted smoothly with enone **2** and amine **3** under optimized conditions to afford unsymmetrical bicyclic ring fused tetrahydropyridines in moderate yields (Scheme 2).

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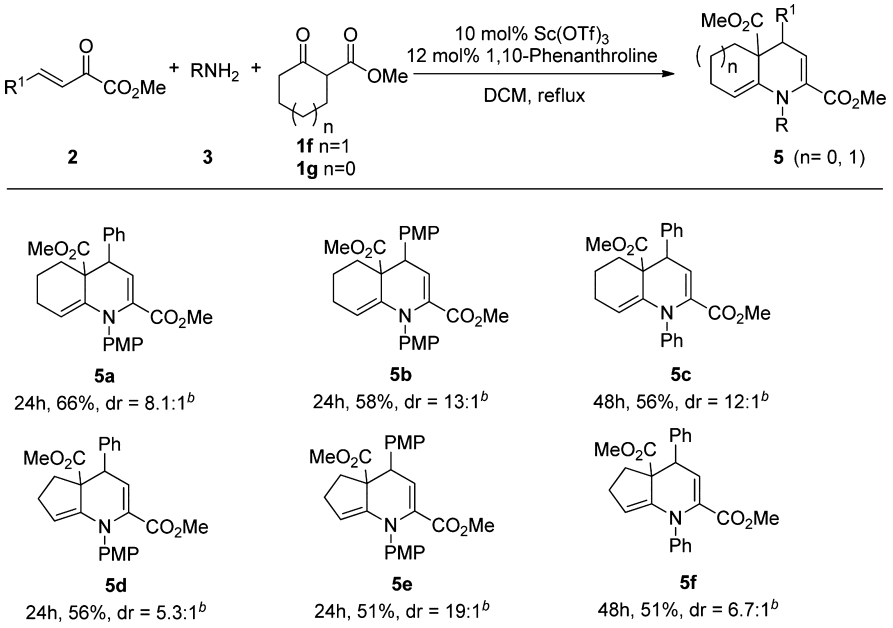
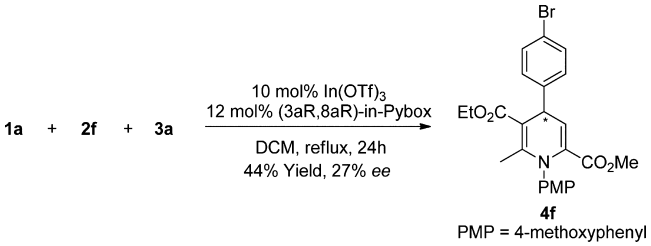
Scheme 2. Synthesis of Tetrahydropyridines[a]



[a]Under argon, reactions were carried out with 0.24 mmol of **1**, 0.2 mmol of **2**, 0.24 mmol of **3**, 10 mol % of $Sc(OTf)_3$, and 12 mol % 1,10-phenanthroline in 2 mL of DCM. [b]Yield was isolated yield. dr was determined by ^1H NMR of crude product. PMP = 4-methoxyphenyl.

A preliminary experiment was carried out for an asymmetric version of this reaction. The application of a chiral ligand, i.e., indan-Pybox, only resulted in low enantioselectivity (27% ee) of this reaction in moderate yield (44%) (Scheme 3).

Scheme 3. Preliminary Examination of an Enantioselective Variant



In summary, we have developed a $Sc(OTf)_3$-catalyzed three-component cyclization reaction of arylamines, β,γ-unsaturated α-ketoesters, and 1,3-dicarbonyl compounds, providing facile access to highly substituted dihydropyridines and tetrahydropyridines which are not accessible using existing methods. It is notable that fused bicyclic tetrahydropyridines bearing a quaternary all-carbon center were readily formed using this approach. This method is an ideal complement to the existing methods. The mild conditions, readily available starting materials, and high yields make this protocol useful in organic synthesis.

EXPERIMENTAL SECTION

β,γ-Unsaturated α-ketoesters were prepared according to literature reported procedures.[12] ^1H NMR and ^{13}C NMR spectra were acquired at 500 and 125 MHz in $CDCl_3$. Dichloromethane was distilled from CaH_2 prior to use.

General Procedure. A mixture of $Sc(OTf)_3$ (0.02 mmol) and 1,10-phenanthroline (0.024 mmol) was stirred at room temperature for 2 h in DCM (2 mL). The appropriate 1,3-dicarbonyl compounds **1** (0.4 mmol), β,γ-unsaturated α-ketoesters **2** (0.24 mmol) and amine **3** (0.2 mmol) were then added. The resulting mixture was stirred under reflux. After the reaction was completed, the reaction mixture was purified through column chromatography (silica, eluent: mixture of hexane and ethyl acetate).

ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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