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Enantioselective Organocatalytic Hantzsch Synthesis of Polyhydroquinolines

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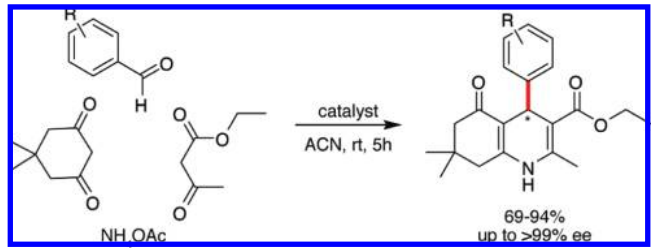
ABSTRACT



The four-component Hantzsch reaction provides access to pharmaceutically important dihydropyridines. To expand the utility of this method, we have developed a route under organocatalytic conditions with good yields and excellent ee's. Through catalyst screening, we found that a BINOL−phosphoric acid allowed enantioselective synthesis of six-membered heterocycles with a variety of substitution patterns.

Multicomponent reactions, such as the Biginelli,[1] Passerini,[2] Ugi,[3] and Hantzsch, provide a wide variety of important heterocycles.[4] For example, the Hantzsch reaction provides dihydropyridines with activity against calcium channels, multidrug resistance (MDR) proteins, 5-hydroxytryptamine (5-HT) receptors, and anti-inflammatory targets.[5] Beyond their pharmaceutical applications, Hantzsch-derived dihydropyridines are also useful as synthetic tools for reducing imines to amines.[6]

While enantioselective examples of the Biginelli,[7] Mannich,[8] and Passerini[9] reactions are well-known, parallel methodologies have not been developed for the four-component Hantzsch reaction. Historically, the harsh conditions required for this reaction, such as refluxing ethanol, have made development of an asymmetric route challenging. For example, attempts to use glycosylated enamines to develop diastereoselective products yielded only modest selectivity (Scheme 1).[10] With more recent advances in Lewis acid catalyzed reactions, one way to achieve enantio-

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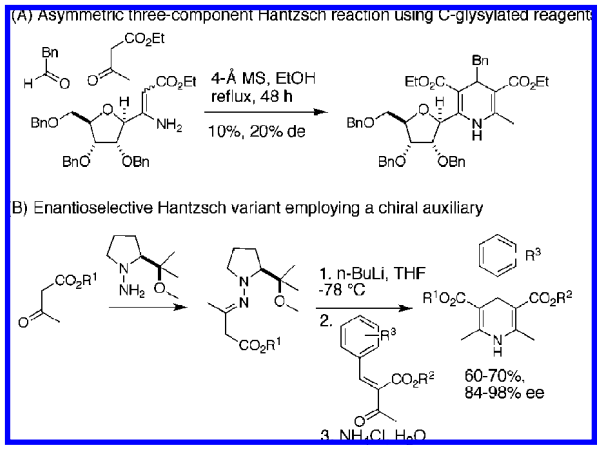
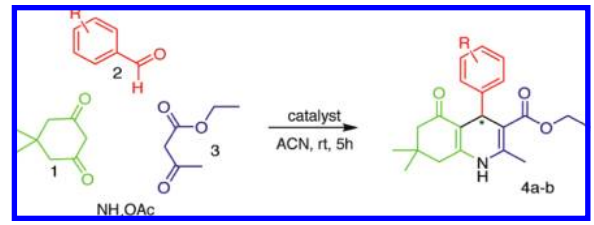
Scheme 1. Current Methodology



enrichment is to use an enamine attached to a chiral auxiliary in the presence of *n*-butyllithium (Scheme 1).[10] While the enrichment values for this method are good to excellent (~84 to 96%), this approach reduces the reaction to three components and limits the diversity of the corresponding products. In this work, we sought to develop a relatively benign and efficient method to produce enantio-enriched, four-component Hantzsch products.

As a model reaction, we selected a known polyhydroquinoline that would afford one stereocenter (Table 1). Consistent with previous reports, 1 equiv of dimedone (0.4 mmol), ethyl acetoacetate, a benzaldehyde, and ammonium acetate, in the presence of $Yb(OTf)_3$ (10 mol %), produced product **4a** in both ethanol and acetonitrile (entries 2−3, Table 1). Workup consisted of precipitating with 1 mL of ice/water, stirring for approximately 1 h, filtering the precipitate, and recrystallizing the product from an ethanol/water system (3:1 vol). Using this procedure, we found good yields (68% in ethanol and 72% in acetonitrile), but the

Table 1. Reaction Optimization



entry	catalyst[a]	solvent	dimedone (equiv)	aldehyde	compd	side product	yield (%)
1	$FeCl_3$	ACN	1	2,4-Cl-Ph	**4a**	yes	62
2	$Yb(OTf)_3$	EtOH	1	2,4-Cl-Ph	**4a**	yes	68
3	$Yb(OTf)_3$	ACN	1	2,4-Cl-Ph	**4a**	yes	72
4	$Yb(OTf)_3$	ACN	0.9	2,4-Cl-Ph	**4a**	yes	53
5	$Yb(OTf)_3$	ACN	1.2	2,4-Cl-Ph	**4a**	yes	79
6	$Yb(OTf)_3$	ACN	1.5	2,4-Cl-Ph	**4a**	no	92
7	$Yb(OTf)_3$	ACN	1.5	Ph	**4b**	no	90
8	$Yb(OTf)_3$°	ACN	1.5	Ph	**4b**	no	52
9	$Yb(OTf)_3$*	ACN	1.5	Ph	**4b**	no	65
10	$Yb(OTf)_3$#	ACN	1.5	Ph	**4b**	no	84

[a] Catalyst concentration: 10 mol % except for 0.1 mol % (o), 1 mol % (*), and 5 mol % (#).

reaction also resulted in formation of the symmetrical side product, which lacked the dimedone. In an attempt to minimize this competing pathway, the equivalents of dimedone were systematically increased (entries 4−6, Table 1). At 1.5 equiv, the yield increased to 90% with concomitant reduction in the side product. Next, we attempted to reduce the catalyst concentration by screening at 5.0, 1.0, and 0.1 mol %. In each case, decreasing the catalyst levels reduced the yield (84, 65 and 52%, respectively; entries 8−10, Table 1). Based on these observations, we selected 10 mol % of catalyst and 1.5 equiv of dimedone for further studies.

Using these conditions, our plan was to screen organocatalysts for those that would afford a high degree of enantioselectivity. A limited number of chiral Lewis acids[11] as well as proline and its derivatives[12] have been explored in this context, but these have produced modest stereoselectivity. Guided by those findings, we focused on a proline-derived catalyst (I) and an expanded series of Lewis acid catalysts (II−VII). To estimate the enantio-enrichment of the products, we used polarimetry in combination with chiral HPLC. Using this approach, we found that catalyst I provided good yields (86%) but no appreciable enrichment. Next, a series of phosphine-based ligands (BINAP−II and −III, DPPF−IV, and DPE−V) was explored. These catalysts were used at 10 mol % with 11 mol % of a cocatalyst, $Pd(OAc)_2$, which provided yields between 75 and 84% but no enantio-enrichment. Finally, we synthesized[13] and explored chiral BINOL−phosphoric acid derivatives (VI and VII). Both catalysts provided good yields (84−85%) and 98% ee (Table 2), suggesting that enantio-enriched dihydropyridines could be assembled by this route.

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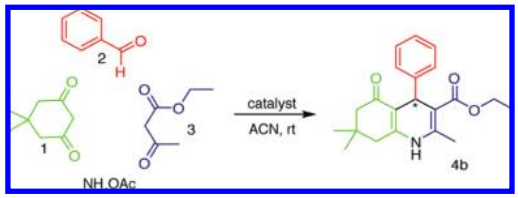
Table 2. Catalyst Screening



entry	catalyst	time (h)	yield (%)	$[\alpha]_D^{20}$ (deg)	% ee
1	$Yb(OTf)_3$	3	90	+ 0.17	-
2	I	5	86	- 0.20	-
3	II	5	82	+ 0.06	-
4	III	5	80	- 0.41	-
5	IV	5	84	+ 0.05	-
6	V	5	75	+ 0.00	-
7	VI	4	84	+ 15	98
8	VII	4	85	+ 16	98

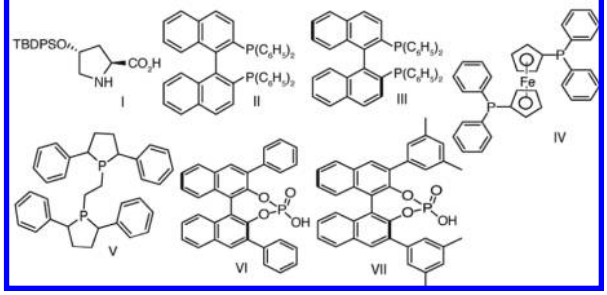
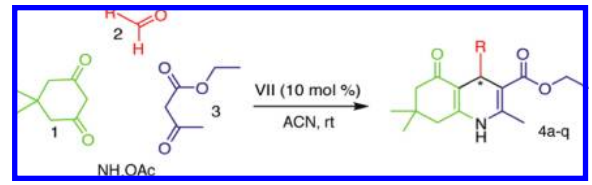


Table 3. Investigation of Reaction Scope



entry	time (h)	aldehyde (R)	compound	yield (%)	$[\alpha]_D^{20}$ (deg)	% ee*
1	3	2,4-ClPh	**4a**	89−94	+3.8	>99
2	4	Ph	**4b**	82−85	+16	98
3	4	4-BrPh	**4c**	80−84	+4.1	96
4	5	3,5-MeOPh	**4d**	72−74	+30	>99
5	3	3-FPh	**4e**	89−92	+23	87
6	5	$4\text{-}(CH_3)_2NPh$	**4f**	75−78	+29	93
7	4	$2\text{-}CF_3Ph$	**4g**	79−85	−4.4	>99
8	3	2,5-FPh	**4h**	90−94	+5.5	>99
9	4	4-tBuPh	**4i**	84−88	+12	97
10	5	2-naphthyl	**4j**	81−83	+8.5	>99
11	5	2-CNPh	**4k**	72	+5.0	99
12	5	3,4-OHPh	**4l**	69	+4.1#	95
13	4	$PhCH_2CH_2-$	**4m**	92−94	+4.2	94
14	3	2-ClPh	**4n**	89−94	+8.6	>99
15	5	$4\text{-}C_6H_5Ph$	**4o**	72−77	+12	>99
16	5	$C_2H_5CH(CH_3)-$	**4p**	66	−0.3	
17	5	CH_3	**4q**	72	+0.7	

* Determined by normal-phase, chiral HPLC on an Astec Chirobiotic V2 column (2-propanol/hexanes). # Optical rotation determined in methanol (all others in chloroform).

One of the expected advantages of an enantioselective four-component Hantzsch reaction is in the synthesis of substituted dihydropyridines. Of particular interest are the 4-aryl-functionalized products, which are employed in many synthetic and medicinal applications.[5,6] Toward this goal, we selected a series of substituted aromatic aldehydes and generated the corresponding polyhydroquinolines (**4a**−**l**,**n**,**o**; Table 3). These experiments revealed that most reactions involving aromatic aldehydes proceed to the expected product in good yield (80−94%), although the aldehydes with unprotected polar groups (e.g., **4k** and **4l**) generally had moderately lower yields (69−72%). Importantly, excellent enantio-enrichment values (87 to >99%) were observed for all of the products arising from aromatic aldehydes. Conversely, reactions involving alkyl aldehydes proceeded in good yield (66−94%), but with no enantio-enrichment. In these cases, the size of the appended functionality appeared to dictate the outcome; bulky substitutions, such as those installed by cinnamaldehyde (**4m**; 94%), resulted in significantly better % ee than smaller groups, such as 2-methylbutyraldehyde (**4p**) or acetaldehyde (**4q**).

In summary, we have developed an enantioselective route for the Hantzsch reaction using a chiral phosphoric acid organocatalyst. This enantioselective route proceeded under relatively mild conditions and resulted in good yields for a range of aromatic aldehydes. This method may find use in the synthesis of medically important dihydropyridines and reagents for enantioselective hydrogenation reactions.

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Supporting Information Available: General experimental methods, HPLC methods, data for determining ee values, optical activity data, and ^1H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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