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Organocatalyzed enantioselective synthesis of 6-amino-5-cyanodihydropyrano[2,3-*c*]pyrazoles

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Abstract

The first enantioselective synthesis of biologically active 6-amino-5-cyanodihydropyrano[2,3-*c*] pyrazoles has been achieved through a cinchona alkaloid-catalyzed tandem Michael addition and Thorpe-Ziegler type reaction between 2-pyrazolin-5-ones and benzylidenemalononitriles. The reaction may also be carried out in a three-component or a four-component fashion via the in situ formation of these two components from simple and readily available starting materials. The desired products were obtained in excellent yields with mediocre to excellent enantioselectivities (up to >99% ee).

Keywords

Dihydropyrano[2, 3-*c*]pyrazole; Pyrazole; Dihydropyrane; Cinchona alkaloid; Organocatalysis; Multi-component reaction; Tandem reaction

Dihydropyrano[2,3-*c*]pyrazole derivatives have very important biological activities, such as anticancer,[1a] antimicrobial,[1b] anti-inflammatory,[1c] insecticidal,[1d] and molluscicidal activities.[1e,f] They are also potential inhibitors of human Chk1 kinase (Fig. 1).[1g] Due to their biological significance,[1] there has been considerable interest in developing synthetic methods for 6-amino-5-cyanodihydro-pyrano[2,3-*c*]pyrazoles.[2–6] These compounds may be readily obtained from the reaction of 4-arylmethylene-5-pyrazolone and malononitrile, [2,3] or 2-pyrazolin-5-ones and benzylidenemalononitriles.[3] The overall reaction is a tandem Michael addition and a Thorpe-Ziegler type reaction (an enol addition to a cyano group) followed by tautomerization.[3] It should be pointed out that these compounds may exist in the 1,4-dihydro or 2,4-dihydro tautomeric forms when the N1 position is unsubstituted. Although most studies assigned the 1,4-dihydro structure to these derivatives,[2–4] recent X-ray crystallographic data prefer the 2,4-dihydro tautomer.[5,6]

Since benzylidenemalononitriles may be synthesized in situ from aromatic aldehydes and malononitrile under the reaction conditions, these compounds may also be synthesized through a three-component reaction of 2-pyrazolin-5-ones, malononitrile, and aromatic aldehydes.[4,5] Most recently, a four-component synthesis by using hydrazine hydrate, acetoacetate, malononitrile, and aromatic aldehydes has also been demonstrated.[6] Nevertheless, to our knowledge, an enantioselective synthesis of these interesting compounds has not yet been realized.[7]

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Supplementary data
Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.210.

During our ongoing research in developing novel organocatalytic enantioselective methods for the synthesis of biologically active compounds,[8] we became interested in the asymmetric synthesis of 6-amino-5-cyanodihydro-pyrano[2,3-*c*]pyrazoles. Herein we wish to report the first enantioselective synthesis of these derivatives through a tandem Michael addition-Thorpe-Ziegler reaction, using some readily available cinchona derivatives as the catalyst.[9]

Initially we studied the synthesis with 3-methyl-2-pyrazolin-5-one (**10a**) and benzylidenemalononitrile (**11a**) as the model substrates. Several readily available cinchona alkaloid derivatives (Scheme 1) were screened as the catalysts. The results are summarized in Table 1.

As shown in Table 1, when quinine (**1**) was used as the catalyst in CH_2Cl_2 at rt, a yield of 80% of the product **12a** was obtained with a low ee value of 23% (entry 1). In contrast, when cupreine (**2**) was used as the catalyst, product **12a** was obtained in high yield of 92% with an excellent ee value of 96% (entry 2). Nevertheless, 9-*epi*-cupreine (**3**) leads to a lower ee value of 65% (entry 3). When 9-*epi*-amino-9-deoxyquinine (**4**) was applied as the catalyst, a racemic product was obtained (entry 4). Similarly, poor enantioselectivities were achieved with quinine-derived thiourea catalysts **5**–**7** (entries 5–7). A low ee value of 22% for the opposite enantiomer was also obtained when quinidine (**8**) was used as the catalyst (entry 8). It is most surprising that cupreidine (**9**), the pseudo-enantiomer of cupreine (**2**), also leads to poor enantioselectivity of the other enantiomer (6%, entry 9). Thus, this screening identified cupreine (**2**) as the best catalyst for the reaction. The results also suggest that the reaction is very sensitive to the subtle changes in the catalyst structure. Further screening of the reaction conditions revealed that chloroform is also a good solvent for this reaction (entry 10), while THF, ether, benzene, and acetonitrile are worse ones (entries 11–14). Lowering the reaction temperature to 0 °C shows no improvement in the enantioselectivity (data not shown). Furthermore, control experiments also indicate that the product does not racemize under the reaction conditions (data not shown).

The absolute configuration of the major enantiomer obtained in Table 1, entry 2 was determined to be *R* according to the X-ray crystallographic analysis of the product **12a** (Fig. 2).[10] Our data also indicate that the product exists in the 2,4-dihydro tautomer form[5,6] in the solid state.

The scope and limitation of this enantioselective synthesis were next examined under the optimized conditions (with 5 mol % catalyst **2** in CH_2Cl_2 at rt).[10] The results are listed in Table 2. As shown by the results in Table 2, besides **11a** (entry 1), other benzylidenemalononitriles also participate in this reaction. However, the enantioselectivity of the reaction drops considerably if there is a substituent on the phenyl ring of the benzylidenemalononitrile. For example, the reaction of *para*-halogen-substituted benzylidenemalononitriles produces the expected products in high yields, but the ee values of the obtained products are only mediocre (48–62% ee, entries 2–5). Other electron-withdrawing groups at the *para*-position, such as, cyano and nitro groups, also lead to low ee values of the products (entries 6 and 7). Electron-donating groups (Me and MeO) at *para*-position also diminish the enantioselectivity of this reaction (entries 8 and 9). By comparing the results in entry 4 and entry 10, it is evident that moving the substituent to the *meta*-position leads to even worse enantioselectivity of the product. These results hint that the enantioselectivity of this reaction is most likely governed by steric factors instead of electronic factors. Moreover, replacing the methyl group in 3-methyl-2-pyrazolin-5-one (**10a**) with a larger ethyl group (**10b**) also leads to much poorer ee value of the product **12k** (38% ee vs 96% ee, entries 1 and 11). Similar results were obtained with the product **12l** of 3-phenyl-2-pyrazolin-5-one (**10c**, entry 12). The use of hexylidenemalononitrile (entry 13) instead of benzylidenemalononitriles also led to a poor ee value (28%) of the product **12m**.

Multi-component reactions involving domino processes allow molecular complexity and diversity to be created by the formation of several new covalent bonds in a one-pot transformation. This methodology has emerged as a powerful synthetic strategy.[12] Most recently, this approach also found many applications in organocatalysis. [13] Since benzylidenemalononitriles (**11**) may be formed in situ from aromatic aldehydes and malononitrile under the reaction conditions,[4,5] we also studied the three-component reaction of **10a**, an aromatic aldehyde (**13**), and malononitrile (**14**). The results are listed in Table 3.[11]

As shown by the results in Table 3, indeed, when cupreine (**2**) was used as the catalyst, the desired product **12a** may be obtained in 80% yield and 96% ee by using **10a**, **14**, and benzaldehyde (**13a**) as the substrates (entry 1). Since 1 equiv of water was formed under the three-component reaction conditions, some drying agents were intentionally added to the reaction mixture to evaluate their effects on the enantioselectivity of this reaction. When 1 equiv of Na_2SO_4 was used, the ee value of the product was improved to 99% ee (entry 2). However, adding 4 Å molecular sieves as the drying agent led to slightly inferior ee value of 94% (entry 3). The yields were also slightly lower in both cases as compared to the reaction without drying agents. Nonetheless, the effects of these additives are more complicated. For example, with *p*-chlorobenzaldehyde (**13c**), molecular sieves prove to give the highest ee value (70%, entry 6) of the product **12c**, which is much higher than those obtained without the additive or with Na_2SO_4 (entries 4 and 5). However, with *p*-bromobenzaldehyde (**13d**), both additives give worse enantioselectivities of the product **12d** (entries 8 and 9) than the reaction without these additives (entry 7). Under these individually optimized conditions, higher ee values of the products may be obtained by using the three-component reaction than by using the two-component reaction (Table 3, entry 2 vs Table 2, entry 1; Table 3, entry 6 vs Table 2, entry 3; Table 3, entry 7 vs Table 2, entry 4).

Next the four-component reaction was studied with cupreine (**2**) by using hydrazine hydrate (**15**) and acetoacetate (**16**) as the precursors for the in situ formation of compound **10a**. The results are listed in Table 4. Benzaldehyde (**13a**) leads to formation of expected **12a** in 28% yield and 16% ee (entry 1). Again various drying agents were evaluated for their effects on the stereoselectivity. Much improved ee values were obtained after adding 1 equiv of $MgSO_4$ or Na_2SO_4, or molecular sieves (entries 2–4) to the reaction mixture, with Na_2SO_4 giving the best results (entry 3). By adding 2 equiv of Na_2SO_4 and carrying out the reaction at 0 °C, a single enantiomer of **12a** may be obtained (entry 5). Similar results may also be achieved in other solvents, such as chloroform (entry 6), acetonitrile (entry 7), and THF (entry 8), except for benzene (entry 9). Whereas this four-component reaction leads to the highest ee value of product **12a**, the yield is considerably lower than the two-component or the three-component reaction. Higher yields may be achieved for other aldehyde substrates, such as *p*-chloro (**13c**), *p*-bromo (**13d**), *p*-nitro (**13g**), and *p*-methoxybenzaldehyde (**13i**), but the enantioselectivities obtained were only low to mediocre (entries 10–13).

In summary, we have developed the first enantioselective method for the synthesis of 6-amino-5-cyanodihydropyrano[2,3-*c*]pyrazoles via a two-component, a three-component, or a fourcomponent reaction using cupreine as the catalyst. The enantioselectivity of this reaction was found to be highly dependent on the reaction conditions and on the structure of the catalysts and the substrates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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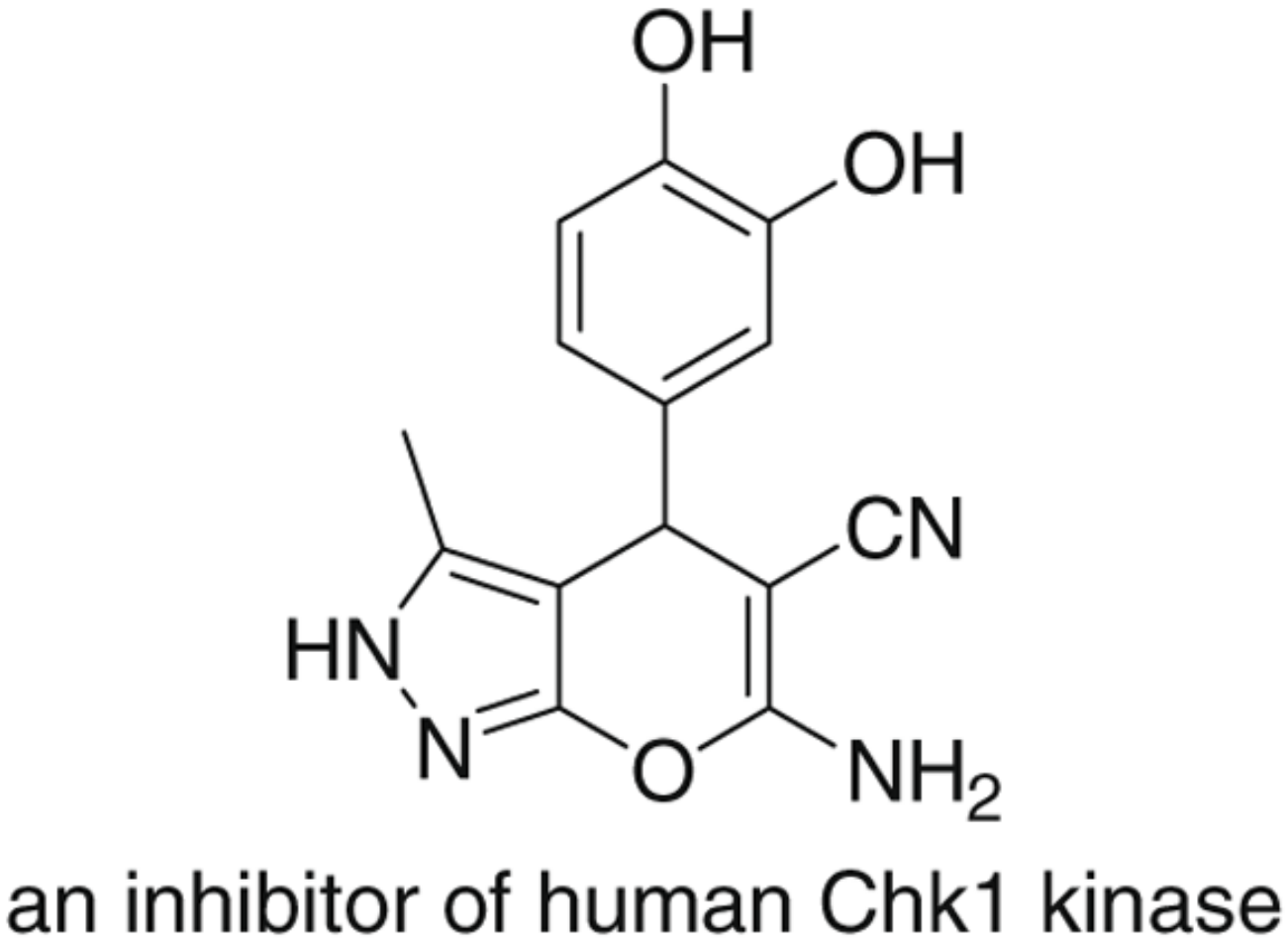


Figure 1.
A biologically active 6-amino-5-cyanodihydropyrano[2,3-*c*]-pyrazole.

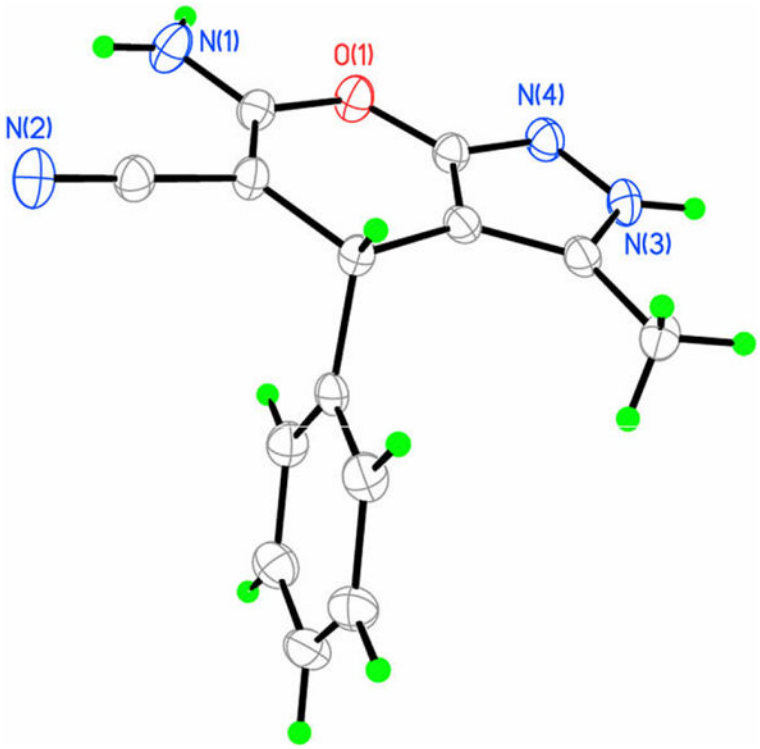
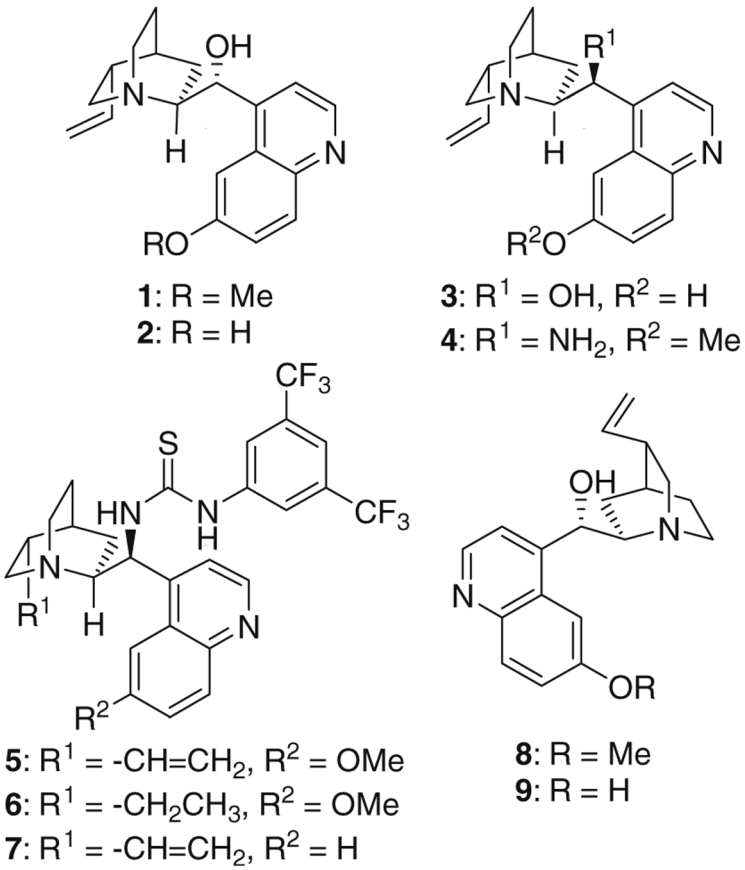


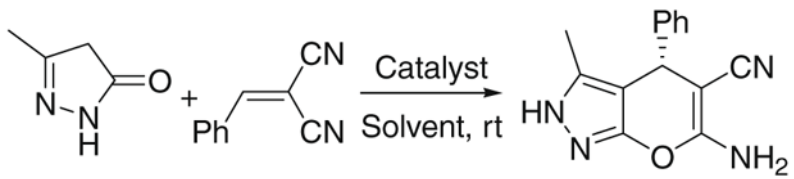
Figure 2.
ORTEP drawing of the product **12a**.



Scheme 1.
Structure of the screened catalysts.

Table 1

Catalyst screening and reaction condition optimization for the two-component reaction[a]



10a **11a** **12a**

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1**	CH_2Cl_2	27	80	23
2	**2**	CH_2Cl_2	24	92	96
3	**3**	CH_2Cl_2	24	91	65
4	**4**	CH_2Cl_2	27	80	0
5	**5**	CH_2Cl_2	27	88	14
6	**6**	CH_2Cl_2	24	79	11
7	**7**	CH_2Cl_2	27	96	10
8	**8**	CH_2Cl_2	27	92	22[d]
9	**9**	CH_2Cl_2	24	83	6[d]
10	**2**	$CHCl_3$	20	87	92
11	**2**	THF	20	74	60
12	**2**	Et_2O	20	94	62
13	**2**	Benzene	20	79	82
14	**2**	CH_3CN	20	91	24

[a] All reactions were carried out with **10a** (0.10 mmol), **11a** (0.10 mmol), and the catalyst (5 mol %) in the indicated solvent (2.0 mL) at rt.

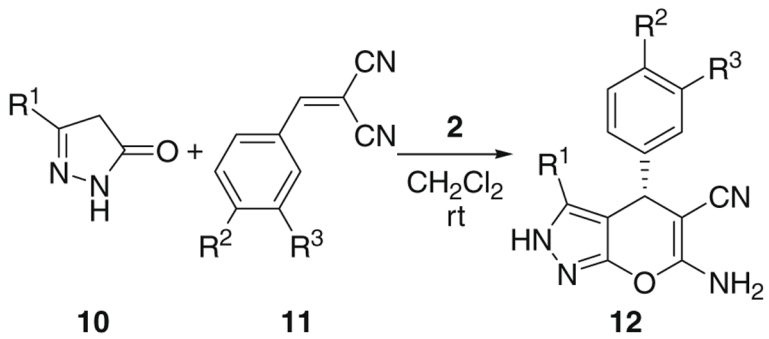
[b] Yield of isolated product after chromatography.

[c] Determined by HPLC analysis on a ChiralPak AS column.

[d] The *S* enantiomer was obtained as the major product.

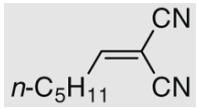
Table 2

Enantioselective two-component reaction for the synthesis of pyranopyrazoles with catalyst **2**[a]



10 **11** **12**

Entry	Compound	R^1	R^2	R^3	Time (h)	Yield[b] (%)	ee[c] (%)
1	**12a**	Me	H	H	27	92	96
2	**12b**	Me	F	H	7.5	96	58
3[d]	**12c**	Me	Cl	H	11	95	62
4	**12d**	Me	Br	H	8	89	50
5[d]	**12e**	Me	I	H	11	94	48
6	**12f**	Me	CN	H	15	92	40
7	**12g**	Me	NO_2	H	14	88	36
8	**12h**	Me	Me	H	15	96	20
9	**12i**	Me	OMe	H	20	96	36
10	**12j**	Me	H	Br	14	92	26
11	**12k**	Et	H	H	12	84	38
12	**12l**	Ph	H	H	17	89	48
13[e]	**12m**	Me			19	79	28



[a] Unless otherwise indicated, all reactions were carried out with **10a** (0.10 mmol), **11a** (0.10 mmol), and the catalyst (5 mol %) in CH_2Cl_2 (2.0 mL) at rt.

[b] Yield of isolated product after chromatography.

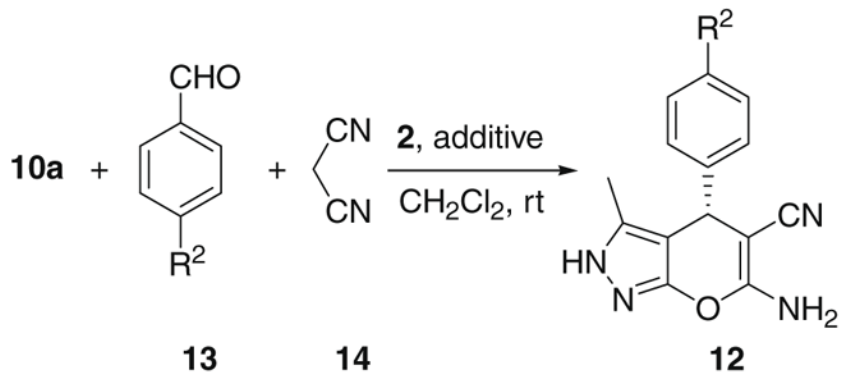
[c] Determined by HPLC analysis on a ChiralPak AS column.

[d] Carried out at 0 °C.

[e] Determined by HPLC analysis on a ChiralPak AD-H column.

Table 3

Enantioselective three-component reaction for the synthesis of pyranopyrazoles with catalyst **2**[a]



13 **14** **12**

Entry	12	Additive	Time (h)	Yield[b] (%)	ee[c] (%)
1	**12a**	—	18	80	96
2	**12a**	Na_2SO_4[d]	25	69	99
3	**12a**	MS(4 Å)[e]	21	72	94
4	**12c**	—	6	54	42
5	**12c**	Na_2SO_4[d]	6	50	34
6	**12c**	MS(4 Å)[e]	6	50	70
7	**12d**	—	6.5	74	66
8	**12d**	Na_2SO_4[d]	23	88	25
9	**12d**	MS(4 Å)[e]	22	89	58

[a] All reactions were carried out with **10a** (0.10 mmol), **13** (0.10 mmol), **14** (0.10 mmol), and the catalyst (5 mol %) in CH_2Cl_2 (2.0 mL) at rt.

[b] Yield of isolated product after chromatography.

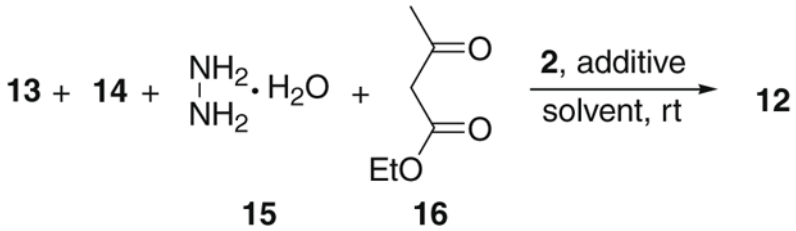
[c] Determined by HPLC analysis on a ChiralPak AS column.

[d] Na_2SO_4 (0.10 mmol) was added.

[e] Molecular sieves (40 mg) were added.

Table 4

Enantioselective four-component reaction for the synthesis of pyranopyrazoles with catalyst **2**[a]



Entry	12	Additive (equiv)	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**12a**	—	CH_2Cl_2	23	28	16
2	**12a**	$MgSO_4$ (1)	CH_2Cl_2	27	21	89
3	**12a**	Na_2SO_4 (1)	CH_2Cl_2	27	25	96
4	**12a**	MS(4 Å)[d]	CH_2Cl_2	27	20	90
5	**12a**	Na_2SO_4 (2)[e]	CH_2Cl_2	28	43	>99
6	**12a**	Na_2SO_4 (2)	$CHCl_3$	24	28	>99
7	**12a**	Na_2SO_4 (2)	MeCN	24	24	>99
8	**12a**	Na_2SO_4 (2)	THF	24	30	98
9	**12a**	Na_2SO_4 (2)	Benzene	24	<5	nd
10	**12c**	Na_2SO_4 (2)	CH_2Cl_2	17	75	23
11	**12d**	—	CH_2Cl_2	21	73	58
12	**12g**	Na_2SO_4 (2)	CH_2Cl_2	17	80	2
13	**12i**	Na_2SO_4 (2)	CH_2Cl_2	18	82	34

[a] Unless otherwise indicated, all reactions were carried out with **13** (0.10 mmol), **14** (0.10 mmol), **15** (0.10 mmol), **16** (0.10 mmol), and the catalyst (5 mol %) in the indicated solvent (2.0 mL) at rt.

[b] Yield of isolated product after chromatography.

[c] Determined by HPLC analysis on a ChiralPak AS column.

[d] Molecular sieves (40 mg) were added.

[e] Carried out at 0 °C.