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Cinchonidinium acetate as a convenient catalyst for the asymmetric synthesis of *cis*-stilbenediamines

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ABSTRACT

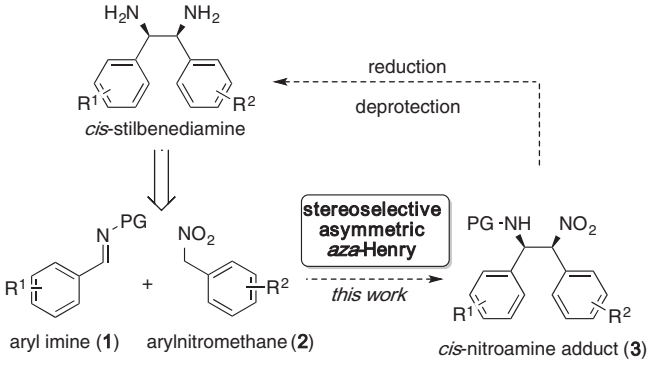
Inexpensive and readily available cinchonidinium acetate is an effective catalyst for the *syn*-selective aza-Henry reaction of arylnitromethanes and aryl imines. The resulting masked *cis*-stilbenediamine products are produced in excellent diastereoselectivity and good enantioselectivity, and enantiopure material can be achieved via recrystallization. The features of the *cinchona* catalyst needed for selectivity are discussed, with specific emphasis on formation of a kinetically controlled *syn*-product without epimerization of the highly acidic α-nitro stereocenter.

Introduction

The vicinal diamine moiety is a central structural feature of many biologically significant molecules, ranging from pharmaceuticals to molecular imaging tools.[1] Moreover, this array serves as the critical stereocontrol element in a substantial percentage of both organo- and metal-based asymmetric catalysts.[2] Despite their utility, asymmetric methods for the synthesis of several classes of vicinal diamines remain challenging, often relying on chiral resolutions.[3] In particular, access to *cis*-stilbenediamines, possessing a *syn*-1,2-diaryl unit, has largely remained limited to symmetric compounds via dimerization methods to form the *meso* diamine.[4] Many of these processes suffer from poor diastereoselection, and all require subsequent chiral resolution to afford enantioenriched diamines. Recently, Seidel has elegantly demonstrated the desymmetrization of *meso*-stilbenediamines via thiourea catalysis, providing monobenzoylated diamines in good ee.[5]

An attractive approach for the enantioselective synthesis of both symmetric and unsymmetric *cis*-stilbenediamines exploits the use of the aza-Henry, or nitro-Mannich, reaction for the union of two nitrogen containing fragments. Specifically, addition of an arylnitromethane nucleophile (presumably as the nitronate) into an aryl imine provides the β-nitroamine adduct, which upon reduction and deprotection reveals the free diamine (Scheme 1).

While considerable success has been achieved for the asymmetric aza-Henry reaction using nitromethane and its alkyl congeners,[6] examples using arylnitromethanes are limited, and largely reveal orthogonal reactivity and stereocontrol when utilized with otherwise well-behaved catalyst systems.[7] In addition to identifying suitable conditions for arylnitromethane reactivity, a key challenge lay in constructing and preserving the highly acidic β-nitro stereocenter. Notably, Johnston and coworkers have reported an elegant process for accessing the *syn* β-nitroamine aza-Henry adducts with high diastereo- and enantiocontrol utilizing a bisamidine-quinoline catalyst, highlighted by the synthesis of the p53-MDM2 inhibitor Nutlin-3.[8] The same group recently revealed a



Scheme 1. Proposed synthesis of *cis*-stilbenediamines via aza-Henry reaction.

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modified monoamidine-amide catalyst to be effective for this transformation on a variety of substrates, although poorer stereocontrol was observed with electron-deficient arylnitromethanes.[9] Herein, we report a complimentary and convenient method for the asymmetric synthesis of *cis*-stilbenediamines using readily available, inexpensive cinchonidinium acetate as the catalyst. This convergent approach provides exceptional diastereocontrol for unsymmetric products as well as good enantiocontrol, and enantiopure material is readily obtained via recrystallization.

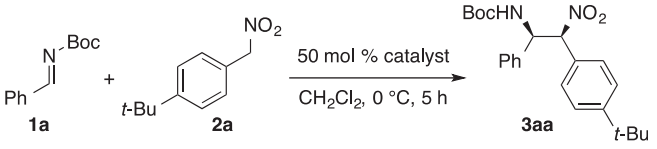
Results and discussion

Initial investigations of the aza-Henry reaction with arylnitromethanes were conducted using BINOL-salen catalysts previously developed in our laboratories.[10] While these systems proved unselective, a survey of Brønsted acids (Fig. 1) led to the discovery of the *cinchona* alkaloid cinchonidinium acetate as a potential stereocontrol platform. Although proline salts **4** and **5** as well as bisamidinium **7** exhibited moderate diastereocontrol (Table 1), they provided essentially racemic nitroamine adduct. Notably, 3,3′-substituted BINOLphosphoric acid **8**, effective in several asymmetric Brønsted-acid catalyzed transformations,[11] yielded only trace product. In contrast, cinchonidinium acetate, formed via protonation of the quinuclidine nitrogen (pK_a AcOH = 4.76, pK_a cinchonidinium–H^+ = 8.40),[12] smoothly provided the desired *syn* product[13] **3aa** with a high 93:7 dr and moderate 61% ee.

Reasoning that the acetate anion plays a role in the asymmetric step, chiral counteranions were examined (Table 2, entries 1 and 2). The similar levels of enantioselection offered by the salts from both enantiomers of **10** pointed away from the counterion being a key controller of the asymmetric environment.[8a] A survey of acids of varying strengths revealed a rather narrow window for optimal selectivity centered on acetic acid. In particular, stronger sulfonic acids, *p*-TsOH and TfOH, inhibited the reaction. Greater success was found by decreasing the reaction temperature, resulting in nearly complete diastereocontrol when performing the reaction at −30 °C. Colder temperatures further increased enantioselectivity, but conversion became problematic, with no product formation at −78 °C after several days. Increasing the acetic acid/catalyst stoichiometry to 3:1 hindered reactivity, whereas a 1:3 ratio resulted in slightly poorer diastereo- and enantiocontrol. Alternative imine protecting groups, including *N*-Ts and *N*-Cbz exhibited diminished reactivity, and afforded the corresponding products in lower selectivity in comparison with *N*-Boc imines **1**.

Effects of catalyst structure were explored using other members of the *cinchona* alkaloid family, as well as synthetically modified

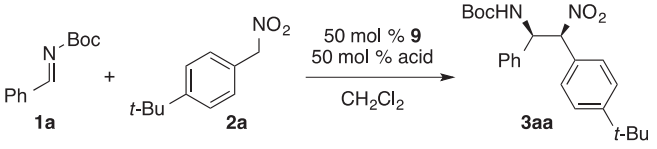
Table 1
Survey of chiral amine and Brønsted acid catalysts



Entry	Catalyst	dr[a] (*syn*:*anti*)	ee[a] (%)
1	**4**	88:12[b]	0(0)
2	**5**	89:11[b]	1(0)
3	**6**	45:55	3(1)
4	**7**[c]	93:7	1(11)
5	**8**[c]	—[b]	—
6	**9**·HOAc	93:7	**61**

[a] Determined by HPLC. Numbers in parentheses refer to ee of the *anti* diastereomer.
[b] Trace product formed.
[c] 25 mol % catalyst used.

Table 2
Optimization of acid additive and temperature



Entry	Acid	pK_a[a] (H_2O)	*T* (°C)	dr[b] (*syn*:*anti*)	ee[b] (%)
1	(*R*)-**10**	1.29[c]	0	88:12	21(44)
2	(*S*)-**10**	1.29[c]	0	88:12	37(45)
3	TfOH	−14[d]	−45	—[e]	—
4	*p*-TsOH	−2.8[f]	0	—[e]	—
5	TFA	0.23	0	86:14	33(25)
6	BzOH	4.20	0	93:7	31(1)
7	*p*-Aminobenzoic acid	4.89	−45	96:4	31
8	AcOH	4.76	0	93:7	61
9	AcOH	4.76	−15	95:5	68
10	AcOH	4.76	−30	97:3	71
11	AcOH	4.76	−45	99:1	74
12	AcOH	4.76	−78	—[e]	—
13	AcOH (150 mol %)	4.76	−45	—[e]	—
14	AcOH (17 mol %)	4.76	−45	98:2	70

[a] Ref. 11.
[b] Determined by HPLC. Numbers in parentheses refer to ee of the *anti* diastereomer.
[c] Value for diphenylphosphate.
[d] Ref. 14.
[e] Trace product formed.
[f] Ref. 15.

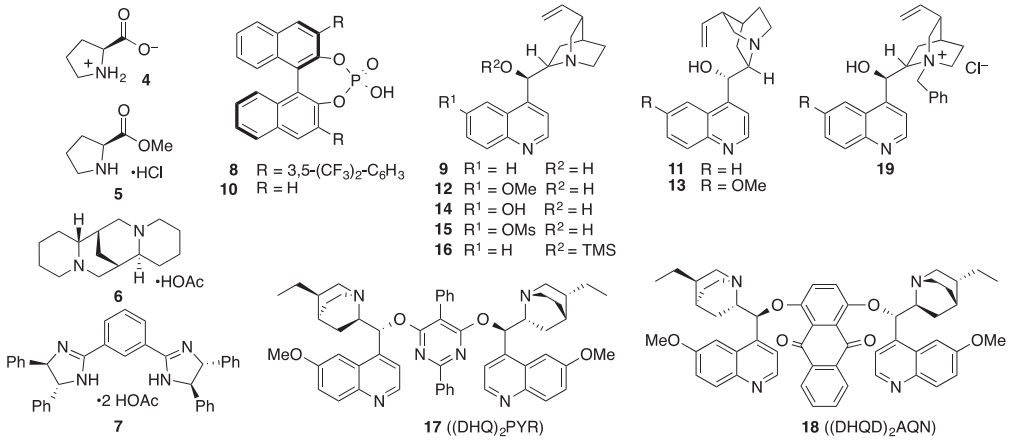


Figure 1. Catalyst structures investigated for the aza-Henry reaction of arylnitromethanes.