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Catalytic Asymmetric [4 + 2] Additions with Aliphatic Nitroalkenes

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Abstract

We describe an unprecedented cycloaddition reaction of 2-pyrones with aliphatic nitroalkenes catalyzed by a new bifunctional cinchona alkaloid-derived catalyst bearing a bulky TIPS-ether at the 9-position. The [2.2.2] bicyclic adducts were obtained in good yield with excellent diastereo- and enantioselectivity. Carbon isotope effects were measured by ^{13}C NMR and are indicative of a stepwise mechanism. Finally, a synthetic application is demonstrated, highlighting the utility of the cycloadducts.

Introduction

Six-membered ring structures are prevalent in natural and synthetic products. Consequently, asymmetric transformations enabling rapid and stereoselective construction of stereochemically defined six-membered rings are of particular importance in organic synthesis. The development of asymmetric [4+2] addition reactions, such as the Diels-Alder reaction, has largely focused on those involving carbonyl-based dienophiles.¹ Nonetheless, asymmetric [4+2] additions with non carbonyl-based dienophiles such as α,β -unsaturated nitriles and nitroalkenes expand upon the range of chiral six-membered ring structures accessible by asymmetric [4+2] additions.² For example, an asymmetric [4+2] addition between a diene and a nitroalkene followed by the reduction of the nitro group³ provides a rapid construction of chiral cyclohexyl amines, a class of highly valuable chiral building blocks (Scheme 1).

Great strides have been made toward the synthesis of functionalized chiral nitrocyclohexanes based on a strategy featuring *in situ* generation of activated dienes from enones via enamine catalysis by chiral amines. Barbas first demonstrated the concept with acyclic enones and aromatic nitroalkenes, albeit in moderate enantioselectivity (38% *ee*).^{2b} Exploring this strategy with 5–7 membered cyclic enones, Cordova obtained high diastereoselectivity and enantioselectivity (>25:1 *dr*, 32–86% *ee*).^{2c} In 2009, Xu developed an improved secondary chiral amine catalyst for this reaction, achieving excellent selectivities with cyclic enones (>25:1 *dr*, 83–96% *ee*).^{2d} Shortly thereafter, Melchiorre reported the use of 9-amino cinchona alkaloids to achieve high selectivities with acyclic enones (2:1 to >19:1 *dr* and 88–99% *ee*).^{2e}

Another successful strategy for the formation of functionalized chiral nitrocyclohexanes involves reaction cascades with nitroalkenes in which Michael addition/aldol reactions are mediated by enamine and iminium catalysis, respectively.^{4,5} The reacting partners of the

nitroalkenes are typically easily enolizable β -ketoesters, γ,δ -unsaturated β -ketoesters, aldehydes, or malonates containing additional electrophilic functionalities.

Notably, these aforementioned asymmetric reactions have so far successfully been applied to almost exclusively aromatic nitroalkenes. To our knowledge, only a single documentation in the literature exists for the formation of a nitrocyclohexane from an aliphatic nitroalkene with synthetically useful selectivity; a tandem Michael/Henry reaction of (E)-2-(nitrovinyl)cyclohexane with 2,5-dihydroxy-3,4-dihydrofuran under the catalysis of a diphenylprolinol silyl ether, developed by Hayashi (45% yield, 99% *ee*).^{5b} Consequently, the development of highly enantioselective and diastereoselective catalytic asymmetric [4+2] additions or ring-forming reaction cascades that are generally applicable to the synthetically important but less active aliphatic nitroalkenes remains an important but challenging task in asymmetric synthesis. In this article, we wish to report a highly diastereoselective and enantioselective [4+2] addition between 2-pyrones and aliphatic nitroalkenes promoted by a cinchona alkaloid-derived bifunctional catalyst.

Results and Discussion

We^{2a,6} and others⁷ have shown that cinchona alkaloids with hydrogen bond donors can promote highly enantioselective and diastereoselective Diels-Alder reactions with inactive but synthetically important 3-hydroxy-2-pyrones in a stereospecific fashion. Thus, we postulated that such bifunctional catalysis may enable us to develop an asymmetric Diels-Alder reaction of 2-pyrones with alkyl nitroalkenes. Accordingly we initiated an investigation aiming at the realization of this transformation.

Our investigation commenced with a catalyst screen (Figure 1) for the model reaction of 3-hydroxy-2-pyrone **6A** with (E)-1-nitro-1-pentene **7a** (Table 1). In the absence of catalyst the reaction did not proceed (entry 1, Table 1), however in the presence of 5 mol% of a natural or modified cinchona alkaloid at room temperature in dichloromethane the reaction readily reached full conversion. Surprisingly, in addition to the expected adducts *endo*-**8Aa** and *exo*-**9Aa**, another stereoisomer of the [4+2] adduct, **10Aa**, was also obtained as a minor product (Table 1). The formation of **10Aa** could arise from a stepwise conjugate addition/aldol reaction cascade (vide infra).

Quinidine **1** afforded low *endo*-selectivity and enantioselectivity (entry 2, Table 1). Quinidine-derived 6'-thiourea catalyst **2** provided *endo*-adduct **8Aa** as the major product but in only 49% *ee* (entry 3, Table 1). Interestingly, a dramatic increase in enantioselectivity was observed with 6'-OH cinchona alkaloid **3a** bearing a benzyl group as the 9-substituent (entry 4 vs. 3, Table 1). However, catalyst tuning via introduction of other aromatic groups as the 9-substituent failed to improve the enantioselectivity (entry 4 vs. 5 and 6, Table 1).

Postulating that a silyl ether group at the 9-position may provide a steric environment different than that presented by aryl-based groups (benzyl, PYR, PHN), 9-silyl ether cinchona alkaloid **4a** was prepared⁸ and utilized to catalyze the model reaction. Gratifyingly, **4a** afforded significantly improved diastereo- and enantioselectivity over those by **3a-c** (entry 7 vs. entry 6, Table 1). The corresponding dihydroquinidine-derived analogue **4b** was found to perform equally well as catalyst **4a** (entry 8 vs. entry 7, Table 1).

To probe the effect of the bulk of the silyl ether on the catalytic selectivity, reactions with silyl ether catalysts **4b-4f** were investigated.⁸ Catalysts derived from larger silyl ethers such as TIPS, TBDPS, and TBS (**4b**, **4c**, and **4d**, respectively) provided similarly high levels of selectivity (entries 8–10, Table 1). On the other hand, smaller silyl ether catalysts such as those derived from TMS and TES (**4e** and **4f**) gave slightly diminished results (entry 11 and 12, Table 1). The highest enantioselectivity could be achieved with triisopropylsilyl

substituted catalyst **4b**. It should be noted that 6'-OH cinchona alkaloids bearing a 9-silyl ether group have not yet been reported in the literature, although both a 6'-thiourea cinchona alkaloid derivative bearing a silyl ether group⁹ and trimethylsilylquinine¹⁰ were reported to be effective catalysts for asymmetric desymmetrization-fragmentations and ketene-aldehyde cycloadditions, respectively.

With optimal catalyst **4b** in hand the remaining reaction parameters were screened. At room temperature THF was found to be the optimal solvent, in which both the diastereoselectivity and the enantioselectivity were noticeably improved (entry 13 vs. 8, Table 1).⁸ Cooling the reaction to -20 °C provided additional increases in both diastereoselectivity and enantioselectivity (entry 14, Table 1). By lowering the reaction concentration to 1.0 M, the reaction proceeded with the highest levels of selectivity to give the *endo*-adduct **8a** in 96% ee and with high *endo/exo* selectivity (entry 15, Table 1).

To gauge the impact of the 6'-OH group on the catalytic selectivity of **4b**, a reaction with the corresponding 6'-OMe cinchona alkaloid **5** was investigated. It was found that both the diastereoselectivity and enantioselectivity deteriorated dramatically (entry 16 vs. 15, Table 1), consistent with the proposal that 6'-OH catalyst **4b** promotes this reaction via bifunctional catalysis.

The substrate scope was explored with respect to both the nitroalkenes and the 2-pyrones (Table 2). Importantly, reactions proceeded cleanly in excellent diastereo- and enantioselectivity with both linear (entries 1–3, Table 2) and branched aliphatic nitroalkenes (entry 4, Table 2). The reaction also tolerates α -branched nitroalkenes, providing adducts **8Ae** and **8Af** with high enantioselectivity but with slightly lower diastereoselectivity (entries 5 and 6, Table 2). It is worth noting that **10** was not observed in reactions with α -branched nitroalkenes as it was with the other nitroalkenes. Both unsubstituted and substituted homobenzyl groups were viable substrates, affording adducts **8Ag** and **8Ah** with good diastereoselectivity and excellent enantioselectivity (entries 7 and 8, Table 2). Additionally nitroalkenes bearing a benzyl protected alcohol (**7i**) or a trimethylsilyl group (**7j**) gave excellent results (entries 9 and 10, Table 2). Finally, substituted 2-pyrones were well tolerated as chloro, bromo, and methyl substitution provided cycloadducts **8Ba**, **8Ca**, and **8Da** with similarly high levels enantio- and diastereoselectivity (entries 11–13, Table 2). Though *endo*-adducts **8** could be readily separated from *exo*-adducts **9**, the separation of **8** and **10** proved unfeasible. In all cases, except where **10** was not produced, a mixture of **8** and **10** was obtained with the ratio of **8:10** ranging from 89:11 to 94:6 as determined by NMR analysis (Table 2).

A synthetic application of this new asymmetric [4+2] addition with aliphatic nitroalkenes is demonstrated in the first enantioselective synthesis of the sphingosine analogue **15**, which displays antiparasitic activities (*L. Amazonensis* IC₅₀ = 0.26 μ M and *T. Cruzi* IC₅₀ = 0.19 μ M) that exceed those of the current clinically used drugs pentamidine (*L. Amazonensis* IC₅₀ = 29.4 μ M) and benznidazol (*T. Cruzi* IC₅₀ = 7.4 μ M).¹¹ These parasites lead to leishmaniasis and trypanosomiasis, diseases that manifest themselves through skin deforming lesions and can lead to death if left untreated. To our knowledge, only one racemic synthesis of **15** has been reported in the literature by del Olmo.¹¹ As shown in Scheme 2, our enantioselective synthesis began with the reduction of a mixture of **8Ac** and **10Ac** (94:6 ratio) to the corresponding amines, which, without purification, were subjected to Boc₂O. The resulting *N*-Boc amine **11**, upon chromatographic purification, was obtained as a pure stereoisomer in 70% yield from **8Ac**. A retro Diels-Alder extrusion of CO₂ from **11** furnished the chiral enone **12**, which was reduced in a highly diastereoselective manner to the corresponding allylic alcohol **13**. Lithium aluminum(tri(*tert*-butoxy)hydride was found to be essential for the high diastereoselectivity as other reducing agents gave

significantly poorer results. Subsequent hydrogenation of crude **13** afforded the desired *N*-Boc amino alcohol **14** as a single diastereomer. Standard deprotection of the Boc-protected amine afforded the desired amino alcohol **15**, the structure of which was confirmed by comparison to an authentic sample prepared via del Olmo's route.⁸

In order to determine whether the cycloadducts were formed through a concerted pathway or a stepwise Michael addition/Henry reaction cascade, we investigated the carbon isotope effects for the [4+2] reaction between pyrone **6A** and nitroalkene **7a** using Singleton's method at natural abundance (Figure 2).¹² If the [4+2] reaction were to proceed via a concerted Diels-Alder pathway, carbon isotope effects would be expected at both the α - and β -positions of nitroalkene **7a** and only products **8Aa** and **9Aa** could be formed, meaning that **10Aa** could conceivably arise via epimerization (Pathway A, Figure 2).¹³ On the other hand, if the reaction were to proceed through a stepwise Michael addition/Henry reaction cascade, a carbon isotope effect would be expected at only one of the alkene carbons of **7a**, depending on which step in the cascade is the rate-determining step, and **8Aa**, **9Aa**, and **10Aa** could be formed (Pathway B, Figure 2).

When the reaction was stopped at 74% conversion, the ¹³C ratio of each carbon in the recovered nitroalkene to the same carbon in virgin nitroalkene was measured using quantitative ¹³C NMR. As shown in Figure 2, the only appreciable carbon isotope effect was observed at the β -position of the nitroalkene [¹³C(recovered)/¹³C(virgin) = 1.043, average of three runs], thus indicating that the [4+2] cycloaddition proceeds through a stepwise mechanism to form adducts **8–10**.⁹

Conclusions

In conclusion, we have developed a new bifunctional cinchona alkaloid-derived catalyst that promotes an unprecedented asymmetric organocatalytic [4+2] cycloaddition reaction between 2-pyrones and aliphatic nitroalkenes. A carbon kinetic isotope effect study proves that the reaction does not occur through a concerted pathway but is instead stepwise. To our knowledge, this is the first example of an asymmetric organocatalytic [4+2] cycloaddition reaction successfully employing aliphatic nitroalkenes as dienophile partners. The synthetic potential of this methodology for the asymmetric synthesis of six-membered cyclic amines was illustrated in the development of a concise enantioselective synthesis of the antiparasitic compound **15**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Cinchona alkaloid catalysts screened.

Figure 2.

Carbon isotope effects (R/R_0) calculated for nitroalkene **7a**. The methyl carbon (value in bold) was taken as the internal standard.

Scheme 1.
Nitrocyclohexene synthesis and common transformations.

Scheme 2.

Enantioselective synthesis of **15**. a) Sn Powder, 1.0 M HCl, THF, 20 °C for 1 h then 60 °C for 1 h; b) Boc_2O , H_2O , THF, 20 °C, 16 h, 70% (2 steps), 96% ee; c) Toluene, 150 °C, 2.5 h, 89%, 96% ee; d) $Li(t-BuO)_3AlH$, THF, 0 °C, 0.5 h; e) Pd/C, H_2 , THF, 20 °C, 4 h, 94% (2 steps); f) TFA, CH_2Cl_2 , 20 °C, 4 h, 96%. THF = tetrahydrofuran, TFA = trifluoroacetic acid.

Table 1

Catalyst screening and reaction optimization.^a

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	8Aa : 9Aa : 10Aa ^b	ee ^c 8 (%)
1	-	CH ₂ Cl ₂	23	24	-	-
2	1	CH ₂ Cl ₂	23	1.5	34 : 62 : 4	9
3	2	CH ₂ Cl ₂	23	4.5	78 : 12 : 10	49
4	3a	CH ₂ Cl ₂	23	4.5	62 : 30 : 8	73
5	3b	CH ₂ Cl ₂	23	3	66 : 23 : 11	74
6	3c	CH ₂ Cl ₂	23	1.5	65 : 29 : 6	78
7	4a	CH ₂ Cl ₂	23	1.5	71 : 21 : 8	88
8	4b	CH ₂ Cl ₂	23	2	72 : 19 : 9	88
9	4c	CH ₂ Cl ₂	23	1.5	73 : 22 : 5	87
10	4d	CH ₂ Cl ₂	23	1.5	72 : 19 : 9	87
11	4e	CH ₂ Cl ₂	23	1.5	69 : 25 : 6	84
12	4f	CH ₂ Cl ₂	23	1.5	68 : 27 : 5	84
13	4b	THF	23	1.5	80 : 14 : 6	92
14	4b	THF	-20	5	80 : 12 : 8	96
15 ^d	4b	THF	-20	20	82 : 8 : 10	96
16 ^d	5	THF	-20	24	69 : 22 : 9	61

^a Unless noted, reactions were performed with 0.10 mmol **6A** and 0.20 mmol **7a** in 50 μ L solvent (2.0 M).

^b Determined by ¹H NMR analysis.

^c Determined by chiral HPLC analysis. See supporting information for details.

^d Reaction was performed with 100 μ L solvent (1.0 M).

Table 2

Substrate scope of D–A reaction with respect to nitroalkenes and 2-pyrones.^a

Entry	R	R'	Product	Temp. (°C)	Time (h)	8 : 9 : 10 ^b	Yield (8 + 10) ^c (%)	8 : 10 ^b	ee ^d 8 (%)
1	H		8Aa	-20	20	82 : 8 : 10	82	92 : 8	96
2	H		8Ab	-20	28	81 : 9 : 10	77	91 : 9	95
3	H		8Ac	0	21	85 : 8 : 7	75	94 : 6	95
4	H		8Ad	-20	28	80 : 9 : 11	81	92 : 8	97
5	H		8Ae	0	46	77 : 23 : 0	74	100 : 0	96

Entry	R	R'	Product	Temp. (°C)	Time (h)	8 : 9 : 10 ^b	Yield (8 + 10) ^c (%)	8 : 10 ^b	ee ^d 8 (%)		
6	H			0	54	78 : 22 : 0	81	100 : 0	96		
7	H			-20	20	74 : 15 : 11	79	90 : 10	96		
8	H			-20	20	74 : 18 : 8	68	92 : 8	95 ^e		
9	H			0	20	79 : 11 : 10	78	89 : 11	96

Entry	R	R'	Product	Temp. (°C)	Time (h)	8 : 9 : 10 ^b	Yield (8 + 10) ^c (%)	8 : 10 ^b	ee ^d 8 (%)
10	H		8Aj	-20	4.5	90 : 3 : 7	77	93 : 7	95
11	Cl		8Ba	0	28	89 : 1 : 10	86	92 : 8	96
12	Me		8Ca	0	17	80 : 12 : 8	56 ^f	91 : 9	96
13	Br		8Da	0	18	90 : 0 : 10	75	90 : 10	98

^{a)} Unless noted, reactions were performed with 0.20 mmol **6** and 0.40 mmol **7** in 200 μ L THF (1.0 M).

^{b)} Determined by ¹H NMR analysis.

^{c)} Isolated yield of **8** + **10**.

^{d)} Determined by chiral HPLC analysis.

^{e)} Absolute configuration determined by X-ray analysis of a single crystal of **8Ah**.

^{f)} Inseparable mixture of **8Ca**, **9Ca**, and **10Ca**.