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Asymmetric Catalytic Conjugate Addition of Acetaldehyde to Nitrodienynes/Nitroenynes: Applications to the Syntheses of (+)-α-Lycorane and Chiral β-Alkynyl Acids

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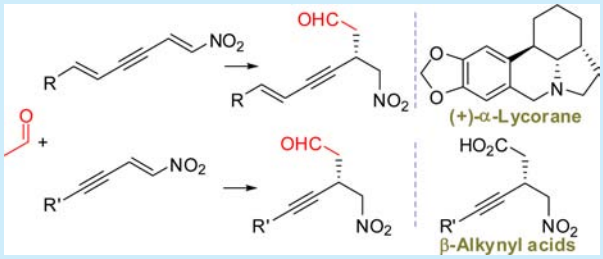
Supporting Information

ABSTRACT: The catalytic enantioselective conjugate addition of acetaldehyde to polyconjugated substrates, nitrodienynes and nitroenynes, has been accomplished using organocatalysis. Various functionalized 1,3-enynes and propargylic compounds were obtained in moderate to good yields with high enantioselectivity. The synthetic utilities of the conjugate addition reactions have been highlighted in the concise total synthesis of (+)-α-lycorane and the metal-free synthesis of chiral β-alkynyl acids.



The direct catalytic asymmetric conjugate addition of carbonyl compounds to electron-deficient alkenes is one of the most powerful tools for carbon−carbon bond formation.[1] Despite remarkable progress, the direct conjugate addition reaction of acetaldehyde, the simplest enolizable carbonyl compound, remains a challenge since acetaldehyde acts as both a highly reactive nucleophile and electrophile, thus leading to its rapid consumption by self-aldolization. Moreover, the addition product possesses a reactive α-unsubstituted aldehyde moiety that can potentially react further to generate several side products.[2] In 2008, the research groups of List and Hayashi independently reported for the first time the asymmetric conjugate addition of acetaldehyde to nitroolefins using organocatalysis.[3] Subsequently, several works on organocatalytic reactions involving acetaldehyde and nitroolefins have been reported.[4] In these previous reports, however, only simple, nonfunctionalized β-nitroolefin substrates were used. Therefore, the potential applications of these reactions are severely limited.

In recent years, the conjugate addition of polyconjugated substrates using metal catalysis and organocatalysis have received increasing attention.[5] However, the corresponding conjugate addition with acetaldehyde as a nucleophile remains elusive,[6] despite the potential utility of the resulting products. Thus, we commenced studies on this topic. In this context, we first selected conjugate nitrodienynes recently introduced by our group[7] as polyconjugated substrates to react with acetaldehyde since such a process would provide an unreported, catalytic method to 1,3-enynes, which are important structural motifs found in many natural products and drugs,[8] as well as versatile building blocks for organic synthesis.[9]

Very recently, we have reported the enantioselective nickel-catalyzed conjugate addition of 1,3-dicarbonyl compounds to nitrodienynes.[7] Herein we describe the first conjugate addition of acetaldehyde to nitrodienynes. This process, which is catalyzed by a simple and commercially available chiral organocatalyst, provides various highly functionalized 1,3-enynes in moderate to good yields with high enantioselectivity. The utility of this conjugate addition is illustrated in the context of application to the concise total synthesis of (+)-α-lycorane. In addition, the conjugate addition of acetaldehyde can be extended to other polyconjugated substrates such as nitroenynes. Based on the development of this reaction, the metal-free, organocatalytic synthesis of chiral β-alkynyl acids has been achieved.

Chiral β-alkynyl acids represent an important class of pharmaceutical compounds with diverse biological activities, including PDE IV inhibitors, TNF inhibitors, GPR40 receptor agonists, and GRP receptor antagonists.[10] However, their asymmetric synthesis remains a significant challenge. To date only several asymmetric syntheses have been reported.[11] Nevertheless, all these syntheses require the use of transition metals in the key chiral center generation step. Removing residual metals from the reaction mixtures is an important issue in the pharmaceutical industry. Thus, the development of a metal-free asymmetric synthesis of β-alkynyl acids is highly desirable. To our surprise, there are no reports of a metal-free, organocatalytic asymmetric synthesis of this important class of compounds[12] despite the obvious advantages of organocatalysis.[13]

The conjugate addition reaction of acetaldehyde with nitrodienyne **1a** was selected as the model reaction (Table 1). Catalyst screening indicated diarylprolinol silyl ethers[14] were suitable catalysts (entries 2−6). Interestingly, trifluor-

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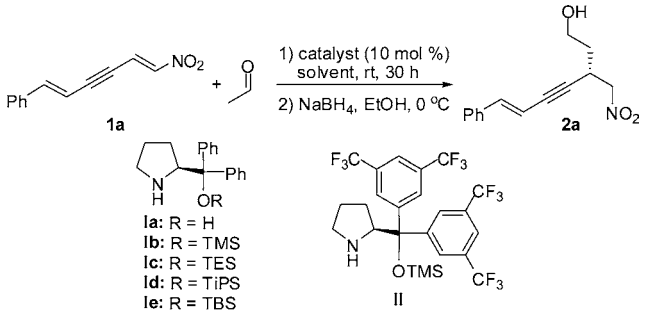
Table 1. Screening and Optimization of Organocatalysts and Solvents



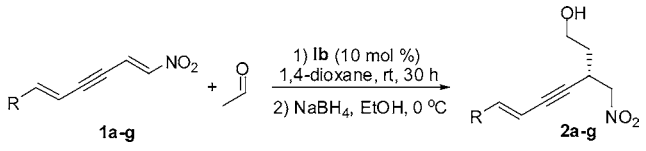
entry	catalyst	solvent	yield (%)[a]	ee (%)[b]
1	**Ia**	1,4-dioxane	trace	N. D.
2	**Ib**	1,4-dioxane	81	93
3	**Ic**	1,4-dioxane	60	90
4	**Id**	1,4-dioxane	70	94
5	**Ie**	1,4-dioxane	80	94
6	**II**	1,4-dioxane	70	94
7	**Ib**	THF	60	95
8	**Ib**	$CHCl_3$	56	81
9	**Ib**	CH_3CN	55	88
10	**Ib**	EtOH	60	93

[a]All reactions were performed at the 0.2 mmol scale using 10 equiv of acetaldehyde with 10 mol % of catalyst. [b]Determined by chiral HPLC.

omethyl-substituted diarylprolinol silyl ether **II**, which was a less reactive organocatalyst in the conjugate addition of acetaldehyde to β-nitroolefins,[3] was effective and provided the conjugate addition product **2a** in good enantioselectivity and yield (entry 6). Finally, simple and commercially available chiral diphenylprolinol trimethylsilyl ether **Ib** was selected as the organocatalyst. Further optimization by variation of the solvent was conducted, and 1,4-dioxane gave the best results. The use of ethanol as solvent also provided good enantioselectivity and yield (entry 10).

With the optimized reaction conditions in hand, the reaction scope was then examined. As shown in Table 2, aryl-substituted nitrodienynes bearing both electron-rich and -deficient aryl groups provided highly functionalized 1,3-enyne products in good yields with high enantioselectivity (entries 2−5).

Table 2. Catalytic Asymmetric Conjugate Addition of Acetaldehyde with Various Nitrodienynes

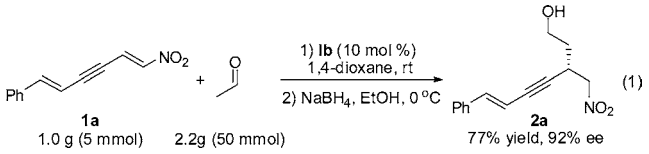


entry	R	product	yield (%)[a]	ee (%)[b]
1	C_6H_5	**2a**	81	93
2	4-MeO-C_6H_4	**2b**	61	84
3	1,3-benzodioxole	**2c**	65	95
4	3-Me-C_6H_4	**2d**	65	85
5	4-Cl-C_6H_4	**2e**	70	98
6	2-thienyl	**2f**	75	86
7	Me	**2g**	51	88

[a]All reactions were performed at the 0.2 mmol scale using 10 equiv of acetaldehyde with 10 mol % of catalyst. [b]Determined by chiral HPLC.

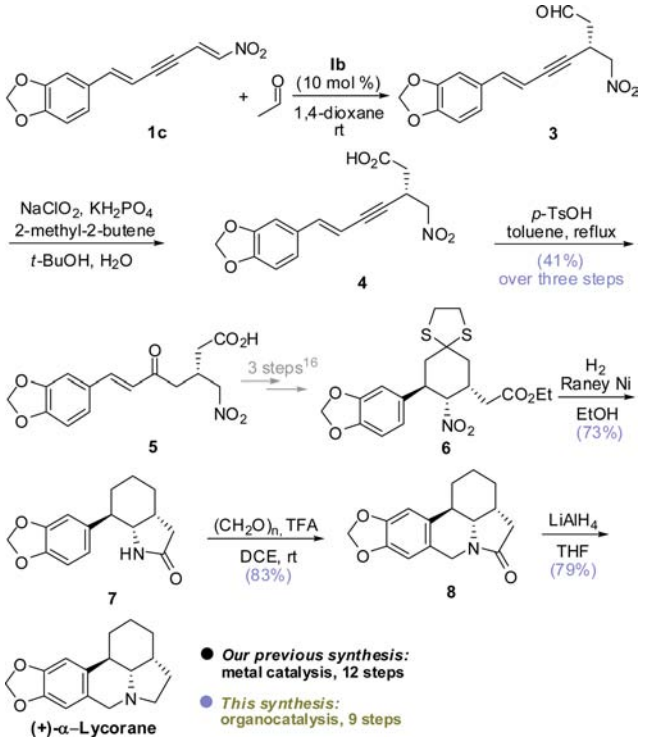
Heteroaryl-substituted nitro dienyne was also a suitable substrate (entry 6). Notably, alkyl-substituted nitrodienyne also afforded the corresponding product in good enantioselectivity, albeit in moderate yields (entry 7). It is noteworthy that no 1,6- or 1,8-addition was observed in all cases.

The catalytic asymmetric conjugate addition of acetaldehyde to nitrodienynes could be performed on a gram scale (eq 1).



The presence of multifunctional groups such as nitro, formyl, and enyne groups makes the conjugate addition products obtained here important chiral building blocks in complex molecule synthesis. The utility of the products was demonstrated by the enantioselective total synthesis of (+)-α-lycorane. There are only three asymmetric formal or total syntheses of (−)-α-lycorane.[15] Very recently, our group described the total synthesis of (+)-α-lycorane, with a key nickel-catalyzed enantioselective conjugate addition of di-*tert*-butyl malonate.[16] We envisioned that the conjugate addition product **3** would provide a suitable framework for the more concise, second-generation total synthesis of (+)-α-lycorane using organocatalysis. As shown in Scheme 1, Pinnick oxidation[17] of chiral **3**

Scheme 1. Organocatalytic Enantioselective Total Synthesis of (+)-α-Lycorane



followed by TsOH-mediated alkyne hydration provided α,β-enone acid **5**, an intermediate previously employed in our first-generation synthesis of (+)-α-lycorane. Following the procedure utilized in the first-generation synthesis of (+)-α-lycorane,[16] compound **5** was transformed into functionalized cyclohexane **6** by a three-step sequence. With **6** in hand, we

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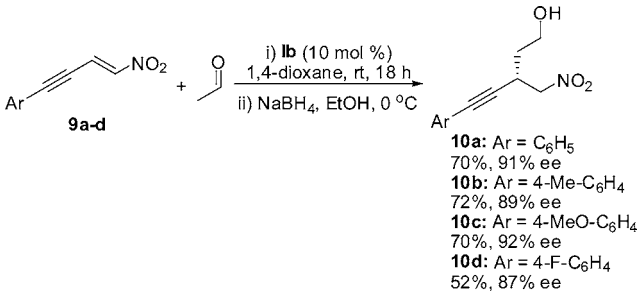
took a significantly improved route which was different from the first-generation campaign. Hydrogenation of **6** with Raney nickel resulted in the direct formation of bicyclic lactam **7**, where a three-step, one-pot cascade reaction involving removal of thioketal, reduction of the nitro group, and cyclization occurred. Then **7** underwent a Pictet−Spengler-type cyclization followed by $LiAlH_4$ reduction which afforded (+)-α-lycorane. All of the spectroscopic data for synthetic (+)-α-lycorane were in accordance with the data reported previously.[15c]

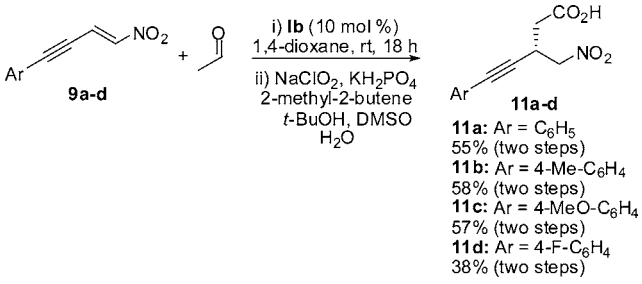
Finally, the catalytic asymmetric conjugate addition reactions of acetaldehyde to other polyconjugated substrates were examined. Although nitrodienes were less suitable substrates, nitroenynes[18] were effective and provided the desired products[19] with a chiral carbon center at the propargylic position[20] (Scheme 2).

Scheme 2. Catalytic Asymmetric Conjugate Addition of Acetaldehyde to Nitroenynes



The conjugate products here were readily converted into functional molecules. In view of the broad synthetic and pharmacological utility of chiral β-alkynyl acids, we became interested in establishing a metal-free route to the compounds of this class. Thus, the conjugate adducts underwent the Pinnick oxidation[17] to furnish the corresponding chiral β-alkynyl acids (Scheme 3). Recently, we also reported an

Scheme 3. Metal-Free, Organocatalytic Synthesis of Chiral β-Alkynyl Acids



enantioselective synthesis of β-alkynyl acids via a nickel-catalyzed conjugate addition of di-*tert*-butyl malonate followed by a TsOH-catalyzed decarboxylation.[11f] However, this approach was not applicable to the synthesis of β-aryl alkynyl acids bearing electron-rich aryl groups since electron-rich aryl alkynes would undergo hydration in the presence of TsOH.[21] In contrast, the organocatalytic method developed here is suitable for the synthesis of various β-aryl alkynyl acids bearing both electron-rich and -deficient aryl groups.

In summary, we have developed the catalytic enantioselective conjugate addition of acetaldehyde to polyconjugated substrates nitrodienynes, providing 1,3-enynes, important structural motifs found in natural products and drugs, in moderate to good yields with high enantioselectivity. The synthetic utility of this reaction has been highlighted in the significantly improved second-generation total synthesis of (+)-α-lycorane. Additionally, the catalytic enantioselective conjugate addition of acetaldehyde to other polyconjugated substrates such as nitro enynes has also been established. Based on the development of this reaction, we have accomplished the metal-free, organocatalytic approach to chiral β-alkynyl acids. This synthesis shows remarkable advantages to previous syntheses of this class of compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and copies of all new compounds. 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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