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A General, Scalable, Organocatalytic Nitro-Michael Addition to Enones: Enantioselective Access to All-Carbon Quaternary Stereocenters

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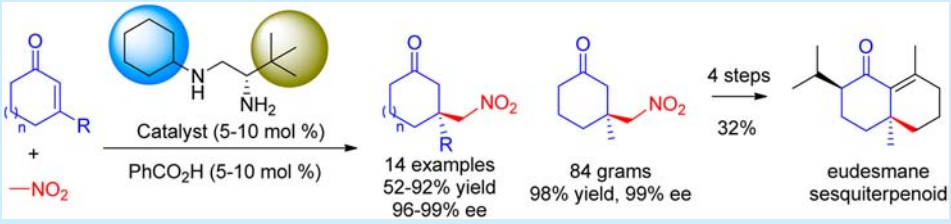
Supporting Information



ABSTRACT: A *tert*-leucine-derived chiral diamine catalyzes the asymmetric Michael addition of nitromethane to five-, six-, and seven-membered β-substituted cyclic enones with excellent enantioselectivity, offering scalable, asymmetric access to all-carbon quaternary stereocenters. The reaction scope can be expanded to include linear acyclic enones, and excellent levels of enantioselectivity are also observed. Furthermore, this organocatalytic, asymmetric nitro-Michael reaction is amenable to multigram scale-up and applications in the construction of an eudesmane sesquiterpenoid skeleton.

The asymmetric construction of all-carbon quaternary stereocenters through efficient carbon−carbon bond forming reactions is a challenging area of organic synthesis.[1] Their stereocontrolled formation plays a vital role in organic chemistry because of the abundance of all-carbon quaternary stereocenters in natural products and drugs. For instance, the skeleton of several sesquiterpenes contains the structural feature shown in Figure 1.[2]

Among the existing methods to build all-carbon quaternary stereocenters, asymmetric conjugate addition (ACA) occupies a prominent position. Asymmetric versions of the reaction can be carried out in the presence of catalytic amounts of chiral ligands and transition metal salts using a range of organometallic species.[3,4] Although transition metals and organometallic nucleophiles have been extensively applied in this transformation, reports describing organocatalytic, metal-free ACA to create all-carbon quaternary stereocenters are still scarce. Nitroalkanes can be used as soft carbon pronucleophiles to form fully substituted stereocenters by addition into β,β-disubstituted enals[5] or enones.[6] To date, the organocatalytic asymmetric nitro-Michael reaction has been mainly limited to cyclic unactivated enones without β-branching with very few exceptions.[6] Recently, Kwiatkowski and co-workers demonstrated the beneficial effect of high pressure (10 kbar) on the challenging organocatalytic asymmetric conjugate addition of nitroalkanes to sterically congested β,β-disubstituted enones.[6d,f] Although good reaction rates and enantiocontrol can be obtained, the high-pressure setup limits utility and prevents easy scale-up of the reaction.

To circumvent the need for external pressure, we envisioned a strategy in which a diamine organocatalyst of general structure **4** (Figure 2) would be able to bring reaction partners in close proximity, covalently binding the enone carbonyl group (iminium formation) and at the same time delivering the nitro compound. We speculated that the secondary amine function would provide the most beneficial hydrogen bonding capability

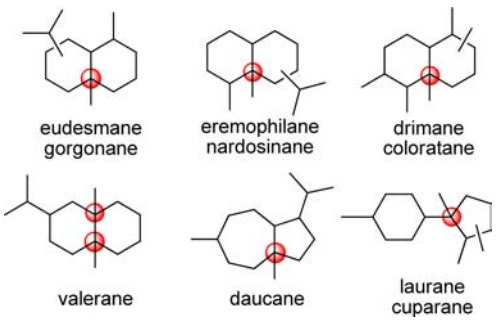


Figure 1. Selected examples of bicyclic sesquiterpene skeletons containing all-carbon quaternary stereocenters.

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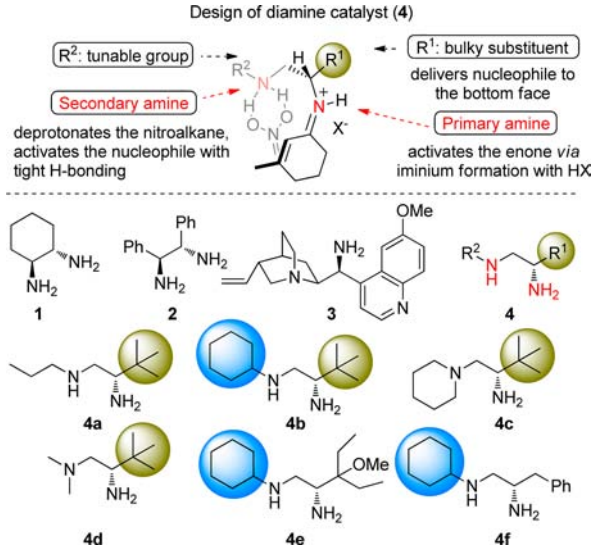
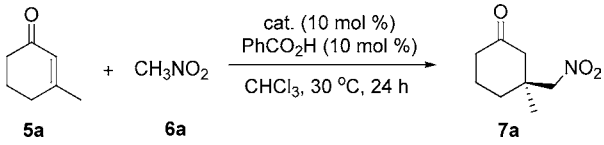


Figure 2. Catalyst design for asymmetric nitro-Michael addition.

for nitroalkane activation through a six-membered H-bonding network.

Aiming for activation and stereocontrol via iminium organocatalysis,[7] we screened the library of primary amines[8] depicted in Figure 2 in a test reaction between 3-methylcyclohex-2-enone (**5a**) and nitromethane (**6a**). Reactions were run for 24 h, and conversion was taken as a crude indication of reaction rate. The primary amines **1**–**3** promoted the reaction with good enantiocontrol but gave rise to prohibitively slow reaction rates (Table 1, entries 1–3). We then turned our attention to a series of more flexible diamines

Table 1. Diamine Organocatalyst Screening in the Michael Addition between 5a and 6a[a]



5a **6a** **7a**

entry	catalyst	solvent	conv (%)[b]	ee (%)[c]
1	**1**	$CHCl_3$	5	86
2	**2**	$CHCl_3$	6	97
3	**3**	$CHCl_3$	11	−99
4	**4a**	$CHCl_3$	2	99[d]
5	**4b**	$CHCl_3$	70	99
6	**4c**	$CHCl_3$	0	
7	**4d**	$CHCl_3$	0	
8	**4e**	$CHCl_3$	33	98
9	**4f**	$CHCl_3$	15	87
10[e]	**4b**	$CHCl_3$	10	96
11[f]	**4b**	$CHCl_3$	15	96
12[g]	**4b**	CH_2Cl_2	97	99
13[h]	**4b**	MTBE	94	99

[a]Reactions performed using 1.0 equiv of **5a** (0.1 mmol, 0.5 M), 4.0 equiv of **6a**, 0.1 equiv of catalyst, and 0.1 equiv of $PhCO_2H$, at 30 °C for 24 h unless otherwise noted. [b]Determined by GC. [c]Determined by HPLC on chiral stationary phase. [d]Measured after 7 days. [e]Without $PhCO_2H$. [f]With 0.2 equiv $PhCO_2H$. [g]With 0.05 equiv of catalyst and 0.05 equiv of $PhCO_2H$ at 40 °C. [h]With 0.05 equiv of catalyst and 0.05 equiv of $PhCO_2H$ at 50 °C.

of type **4** with different substituents. The catalytic performance of diamines derived from *tert*-leucine (**4a**–**d**) turned out to be strongly dependent on the nature of the ancillary (secondary or tertiary) amine moiety. Catalyst **4a** endowed with a propylamine group afforded only 2% conversion over 24 h; however, when the reaction time was extended to 7 days, the enantiomeric excess of **7a** was found to be 99% (entry 4). Pleasingly, catalyst **4b**,[9] with a cyclohexylamine group, allowed the reaction to reach 70% conversion and imparted excellent enantioselectivity (entry 5). No reaction was observed using catalysts **4c** and **4d** (entries 6–7), which possess an additional tertiary amine functionality; this finding supports our speculation regarding the key role of H-bond activation of the nucleophile (Figure 2).

Two more diamines possessing the cyclohexylamino group (**4e** and **f**) were also tested; however, they resulted in lower reaction rates (entries 8–9), thus demonstrating that both the *tert*-leucine scaffold and the cyclohexylamine moiety are required for optimal reactivity. When catalyst **4b** was employed, both the absence of any acidic additive and the use of 20 mol % benzoic acid were detrimental to the reaction rate (entries 10–11).

The effect of solvent was investigated next. All solvents except acetone provided moderate to excellent conversions and outstanding enantioselectivity (see the Supporting Information). With 5 mol % catalyst loading, it was still possible to obtain conversions greater than 90% provided that the reaction temperature was increased to 40 or 50 °C (entries 12–13).

With the optimized reaction conditions in hand, we assessed the scope of the asymmetric Michael addition of nitromethane to various five-, six-, and seven-membered β-substituted cyclic enones for the generation of a quaternary stereocenter. All the reactions proceeded with impressive stereochemical control (96–99% ee) and moderate to good yields (Scheme 1). Most reactions were completed within 48 h, although longer reaction times were required for the nitro-Michael additions to cyclopentenones (**7k** and **l**) and for the reactions of substrates with bulkier groups in the β positions (adducts **7e**, **g**–**i**, and **o**). To enhance the rate of formation of some sterically hindered products (**7g**, **j**, and **l**), the catalyst loading was increased to 20 mol %, and nitromethane was used as solvent.

We next investigated nitro-Michael additions generating two stereocenters. When 3-methylcyclohex-2-enone and 3-methylcyclohept-2-enone reacted with nitroethane to afford adducts **7p** and **q**, respectively, excellent enantioselectivity was observed for both diastereoisomers, but the diastereomeric ratios were close to 1:1, presumably due to facile epimerization of the product nitroalkanes under the reaction conditions.

The absolute configuration of compound **7a**, determined by single crystal X-ray crystallographic analysis on a derivative,[10] is consistent with the model presented in Figure 2.

Our catalytic methodology can be successfully applied to simple, unsubstituted cyclic enones, thus expanding the scope of the protocol (**8a**–**c**). These reactions proceeded with excellent levels of enantioselectivity, although careful choice of experimental conditions was needed to minimize the formation of double Michael addition products and obtain good yields (see the Supporting Information for details).

Good yields and excellent enantiocontrol were also achieved in the nitro-Michael addition reactions to a range of β-alkyl and β-aryl acyclic enones (**8d**–**l**). The reactions of nitromethane with α,β-unsaturated, α'-methyl ketones were complete in 36–

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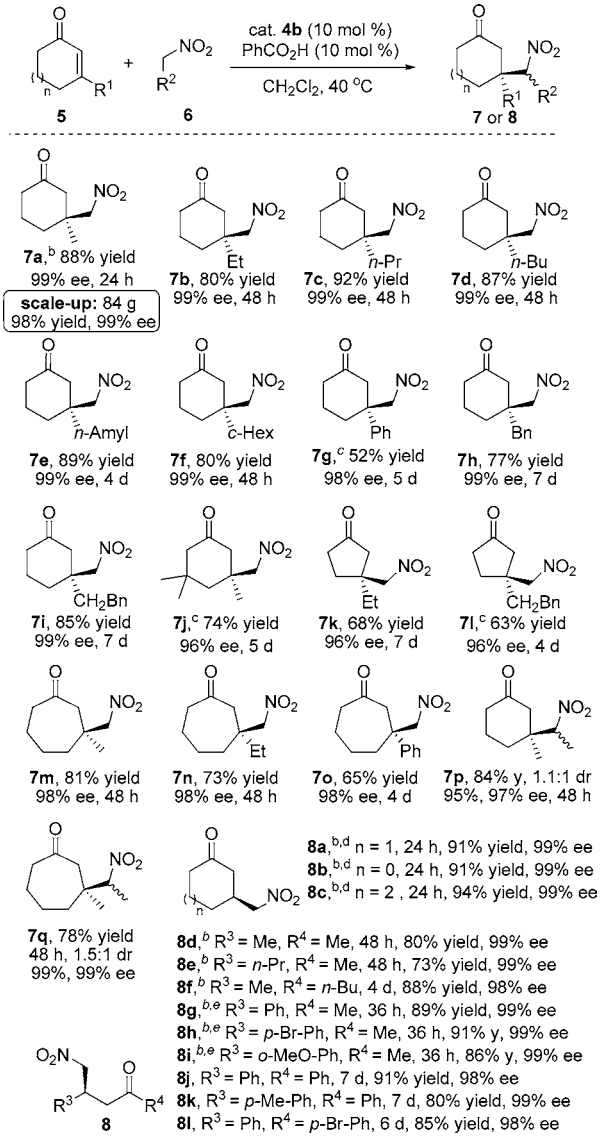
Scheme 1. Scope of the Asymmetric Nitro-Michael Addition to Five-, Six-, and Seven-Membered β-Substituted Cyclic and Acyclic Enones[a]



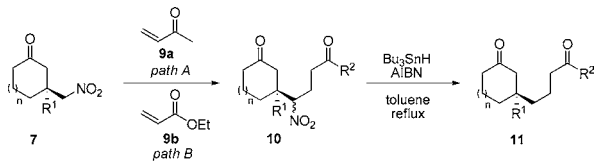
[a]Reactions performed in CH_2Cl_2 at 40 or 30 °C (only for **8a–i, k–l**) using 1.0 equiv of **5** (0.4 mmol, 0.5 M), 4.0 equiv of **6**, 0.1 equiv of **4b**, and 0.1 equiv of $PhCO_2H$ unless otherwise noted. Isolated yields are given. Dr determined by GC. Ee determined by HPLC on chiral stationary phase. [b]With 0.05 equiv of **4b** and 0.05 equiv of $PhCO_2H$. [c]With 0.2 equiv of **4b** and 0.2 equiv of $PhCO_2H$ in CH_3NO_2. [d]In CH_3NO_2 (0.5 M). [e]In AcOEt (0.5 M).

48 h, whereas enones with bulkier residues in the α' position required longer reaction times (**8f, 8j–l**).

A large scale preparation **7a** was performed to investigate scale-up suitability. In the presence of 5 mol % catalyst, 84 g of product were obtained with 98% yield and 99% ee without the need for chromatographic purification.

The applicability of this methodology was demonstrated by the expeditious construction of a eudesmane sesquiterpenoid skeleton. Initially, Michael additions between the nucleophilic C-7 and simple α,β-unsaturated compounds, such as methyl vinyl ketone (MVK, **9a**) and ethyl acrylate (**9b**), were carried out. Extensive screening of the conditions revealed that the reaction of **7a** with MVK could be promoted using K_2CO_3 in dioxane; the MVK Michael addition could be extended to ethyl homologue **7b** and cycloheptanone analogue **7m** to give the desired adducts **10** (Table 2, entries 1–3). Addition of **7a** to

Table 2. Michael Addition of 7 with Methyl Vinyl Ketone and Ethyl Acrylate[a]



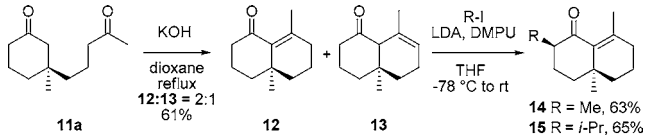
entry	substrate	n	R^1	R^2	product	yield (%)[b]
1	**7a**	1	Me	Me	**11a**	81
2	**7b**	1	Et	Me	**11b**	50
3	**7m**	2	Me	Me	**11c**	55
4	**7a**	1	Me	OEt	**11d**	75

[a]Path A: **7** (1 equiv, 0.1 M), **9a** (2 equiv), and K_2CO_3 (1.2 equiv) in dioxane at rt for 36 h. Path B: **7** (1 equiv, 0.1 M), **9b** (2 equiv) and TMG (1 equiv) in CH_3CN at rt for 48 h. [b]Isolated yield over two steps given.

ethyl acrylate required stoichiometric TMG in CH_3CN as the promoter (Table 2, entry 4). Subsequently and in all cases, the nitro group was removed smoothly with Bu_3SnH/AIBN, affording dicarbonyl compounds **11a–d**.

The desired aldol condensation of **11a** (Scheme 2) was found to proceed in refluxing dioxane using 1 equiv of solid

Scheme 2. Construction of a Sesquiterpenoid Skeleton



KOH, affording a 2:1 mixture of **12** and **13** in 61% yield. Regioselective α-alkylations of this mixture provided compounds **14** and **15** in moderate yields, the latter being a precursor to eudesmane sesquiterpenes (Figure 1).[11]

In summary, a powerful organocatalytic methodology to generate all-carbon quaternary stereocenters operating via Michael addition of nitroalkanes to β-substituted cyclic enones under mild conditions has been developed. The feasibility of scale-up was demonstrated using fairly low catalyst loadings (5 mol %) without affecting the excellent levels of enantiocontrol. The nitro-Michael adducts can be readily elaborated into interesting sesquiterpenoid skeletons. More thorough studies on the large scale application of this organocatalytic methodology are ongoing in our laboratories, and the findings will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Nitro-Michael additions, large scale Michael additions, sesquiterpenoid skeleton syntheses, HPLC traces and NMR spectra of Michael addition products, and determination of absolute configuration. 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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(10) See Supporting Information for details. CDCC 917399 (**7a′**, an indole derivative of **7a**) contains the crystallographic data for this paper. These data can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) The configuration of **15** was assigned by comparison of the NMR data with Chen, K.; Ishihara, Y.; Galán, M. M.; Baran, P. S. *Tetrahedron* **2010**, *66*, 4738. The configuration of **14** was assigned by analogy to **15**.

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