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An Approach to Skeletal Diversity Using Functional Group Pairing of Multifunctional Scaffolds

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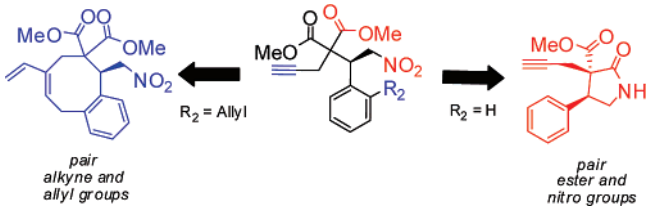
ABSTRACT



Diversification of enantioenriched Michael adducts through functional group pairing to gain access to a range of five- to ten-membered complex fused and bridged ring systems is described.

Diversity-oriented synthesis (DOS) involves preparation of structurally diverse collections of compounds with the aim of discovering small molecule protein modulators.[1a−e] To further develop this strategy, methodologies that allow for the preparation of enantioenriched compounds with high levels of skeletal diversity are needed.[1b] Synthetic approaches toward this goal have successfully explored skeletal rearrangement,[1i] convergent synthesis,[1f,g] "folding" processes,[1h] and linear sequences.[1j] We sought to address this overall objective through synthetic approaches involving selective pairing of two functional groups of interest strategically placed on multifunctional, enantioenriched scaffolds.[2] Skeletal diversity may be achieved by chemoselective activation of different pairs of functional groups in transformations of interest. Similar use of multifunctional enyne scaffolds has recently been reported by Schreiber and co-workers.[2b]

Our overall strategy is outlined in Figure 1. Deng and co-workers recently demonstrated that readily available, modified Cinchona alkaloids are effective catalysts for enantioselective Michael addition of 2-substituted 1,3-ketoesters to β-nitrostyrenes.[3] We envisioned that expansion of this methodology would permit access to highly functionalized modular scaffolds[4] (cf. **1**, Figure 1) suitable for functional group pairing studies and overall investigation of their

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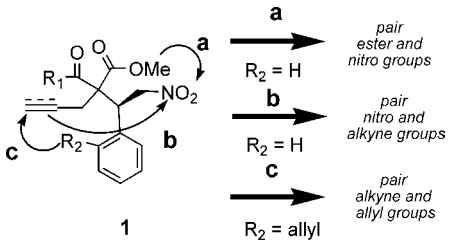


Figure 1. Skeletal diversity through functional group pairing.

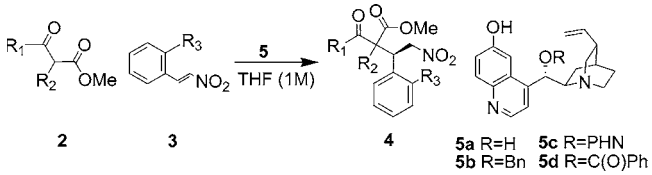
synthetic utility to produce novel structural types. For example, in generalized structure **1**, the nitro group may be paired in chemical reactions with the ester functional group or with the alkyne. Likewise, incorporation of an *o*-allyl moiety into nitrostyrene **1** (Figure 1, R_2 = allyl) enables pairing between R_2 and the alkyne/alkene. In this manner, structurally distinct carbon skeletons may be produced depending on the two functional groups paired. In this Letter, we report the diversification of enantioenriched Michael adducts through functional group pairing approaches to access a range of five- to ten-membered complex fused and bridged ring systems.

We began our study with preparation of the requisite scaffolds (Table 1). Our initial efforts were focused on expansion of the scope of the asymmetric conjugate addition methodology to acyclic substituted malonates bearing pendant alkenes and alkynes. Extensive reaction screening identified phenanthrene derivative **5c** as an optimal catalyst for these reactions (entries 1 and 2). Significantly, it was discovered that malonate derivatives with terminal alkynes were also effective substrates in terms of stereoselectivity (entry 4). Allyl-substituted malonate **2e** (entry 5) performed well in terms of stereoselectivity, but with a slower overall reaction rate.

Our initial results encouraged us to investigate the unexplored, stereoselective Michael additions of ortho-substituted β-nitrostyrenes using Cinchona alkaloid derivative **5c** as catalyst. Deng and co-workers have shown that catalysts **5** were tolerant of β-nitrostyrenes bearing halogens in the para position.[3] We considered that nitroarenes substituted in the ortho position with bromide (**3c**), allyl (**3b**), and alkynyl (**3d**) substituents would permit the synthesis of a number of diverse molecules through selective functional group pairings with ortho-substituted aryl functionality. In the event, we found that conjugate addition of nucleophiles to ortho-substituted β-nitrostyrenes occurred with excellent enantioselectivity (entries 6−9). However, substrates **3b**−**d** showed comparatively sluggish reactivity presumably due to steric hindrance. The absolute configuration of adduct **4g** (entry 8) was determined by X-ray crystallography[5] and is consistent with the previously reported transition-state model.[3]

With access to a range of highly functionalized Michael adducts established, we next turned our attention to examination of their synthetic utility in a range of functional group pairings. Selective nitro reduction of **4b** in the presence of the alkyne, followed by cyclization to form the lactam, required extensive optimization (Scheme 1, reaction a) and provided reductive cyclization product **6** in good yield (dr = 12:1). The absolute configuration of lactam **6** was established through NOE analysis of the corresponding alcohol derived through selective reduction with $LiBH_4$.[5] The nitro group of **4c** was also activated toward reaction with the alkyne through intramolecular 1,3-cycloaddition of the derived nitrile oxide[6] (Scheme 1, reaction b) to provide bicyclic isoxazole **7**.[7] Alternatively, nitrile oxide generation[8] of **4d** and subsequent cycloaddition afforded the corresponding isoxazolines in good yield (dr = 1.1:1 (25 °C), dr = 2.6:1 (0 °C)). The stereochemistries of **8** and **9** were assigned by comparison to spectral data reported for (±) **8** and **9**.[9]

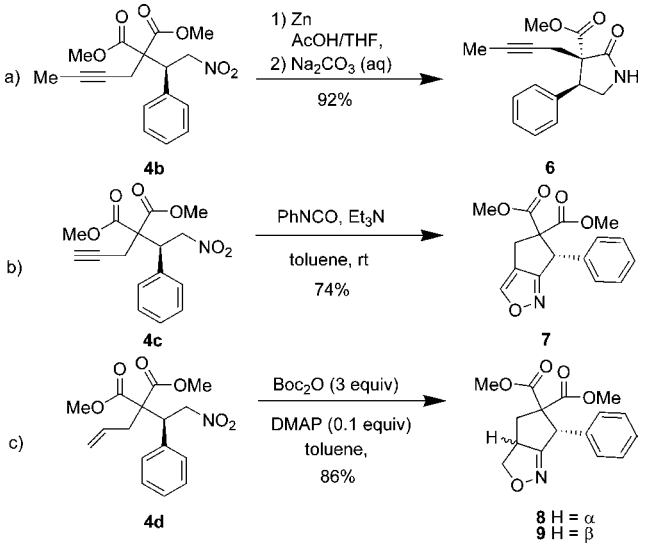
Table 1. Enantioselective 1,4-Addition of Substituted Dicarbonyls to β-Nitrostyrenes[a]



entry	**2**: R_1, R_2	**3**: R_3	cat.	T (°C)	time (h)	conv[b]	yield[c] (%)	ee[d,e] (%)	product
1	**2a**: Me, $CH_2C{\equiv}CH$	**3a**: H	**5a**	−20	16	84	73	99[f]	**4a**
2	**2b**: Me, $CH_2C{\equiv}CH$	**3a**: H	**5c**	−20	48	77	71	98[g]	**4a**
3	**2c**: OMe, $CH_2C{\equiv}CMe$	**3a**: H	**5a**	−20	48	97	85	90	**4b**
4	**2d**: OMe, $CH_2C{\equiv}CH$	**3a**: H	**5c**	−40	3 d	50	45	92	**4c**
5	**2e**: OMe, $CH_2C{=}CH_2$	**3a**: H	**5c**	−20	5 d	51	44	90	**4d**
6	**2d**: OMe, $CH_2C{\equiv}CH$	**3b**: $CH_2C{=}CH_2$	**5c**	−20	168	68	35	95	**4e**
7	**2e**: OMe, $CH_2C{=}CH_2$	**3b**: $CH_2C{=}CH_2$	**5c**	−20	15 d	58	55	92	**4f**
8	**2c**: OMe, $CH_2C{\equiv}CMe$	**3c**: Br	**5c**	−20	5 d	100	87	97	**4g**
9	**2e**: OMe, $CH_2C{=}CH_2$	**3d**: $C{\equiv}CCH_2OMe$	**5c**	−20	5 d	44	41	96	**4h**

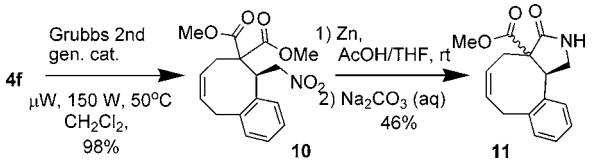
[a] Reactions were conducted (1 M in nitrostyrene) with 2 equiv of the nucleophile and 10 mol % of catalyst. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture (ratio of nitro styrene to product). [c] Isolated yield of product after silica gel chromatography. [d] Determined by HPLC analysis. [e] ee of the major diastereomer. [f] dr of 1.6:1 as determined by ^{1}H NMR analysis. [g] dr of 2.4:1 as determined by ^{1}H NMR analysis.

Scheme 1. Skeletal Diversity through the Pairing of (a) Nitro-Ester, (b) Nitro-Alkyne, and (c) Nitro-Alkene Functional Groups



The ability to construct Michael adducts containing *o*-allyl phenyl groups with high enantioselectivity (Table 1, entries 6 and 7) enabled evaluation of ring-closing metathesis (RCM) (Scheme 2). Thus, when **4f** was microwaved in the presence

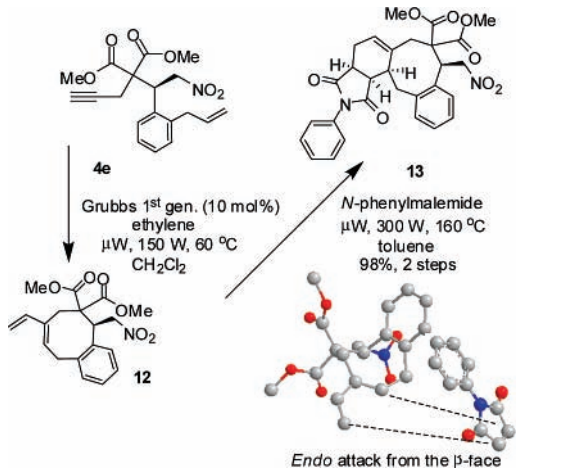
Scheme 2



of Grubbs' second generation catalyst,[10] cyclooctene derivative **10** was formed in high yield. Reductive cyclization of **10** (Scheme 2) provided tricyclic lactam **11** as a mixture of diastereomers (dr = 1.5:1).

We next investigated diversification of the multifunctional scaffolds using enyne metathesis.[2b] We discovered that the reaction (Scheme 3) was highly efficient in the presence of ethylene gas (Mori's condition[11]) and was compatible with microwave heating. Diene **12** was utilized directly in [4+2] cycloaddition with *N*-phenylmaleimide in a one-pot process.[12,13] Interestingly, Diels−Alder cycloaddition of diene

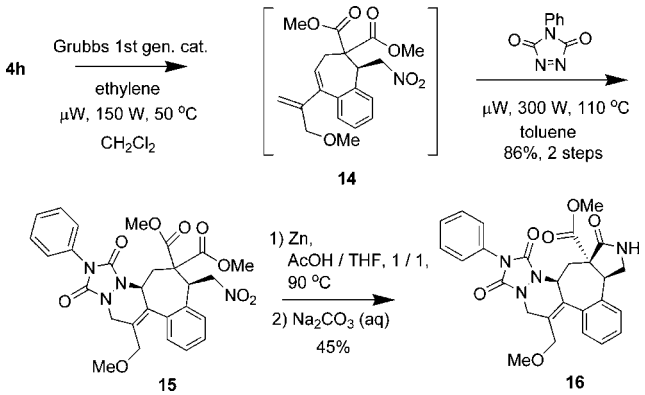
Scheme 3



12 was highly stereoselective (dr = 15:1), with the major diastereomer resulting from endo approach of the dienophile from the same face as the nitro group as determined by NOE experiments.[5] A derived molecular model of **12**[14] (Scheme 3) indicates that the nitro group is directed away from the β face leaving it open to react with the dienophile, while the α face is hindered by one ester group of the malonate moiety.

To access skeletal diversity using enyne RCM, we sought to take advantage of the modularity of the multifunctional scaffolds produced by enantioselective Michael addition and chose to interchange the allyl and alkyne moieties. We therefore subjected **4h** to enyne metathesis conditions to afford the complex diene **14** (Scheme 4), which is structurally

Scheme 4



distinct from **12**. Cycloaddition of **14** with *N*-phenyltriazolinedione afforded the 7-membered fused cycloadduct **15**

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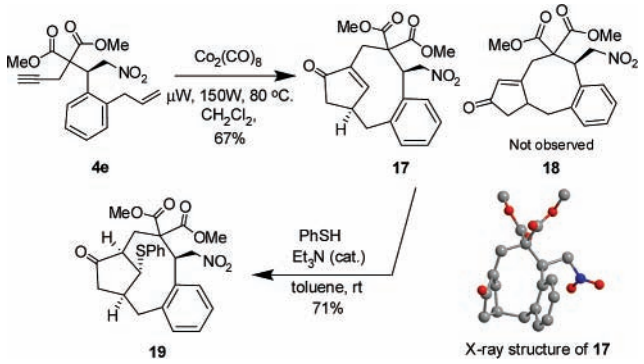
(14) Conformational searches (Merck Molecular Mechanics Force Field (MMFF)) were performed with Spartan '04 Windows (Wavefunction: Irvine, CA).

with complete stereoselectivity. Reductive cyclization of **15** afforded **16**, the stereochemistry of which was established by NOE analysis of the derived primary alcohol.[5]

We next investigated adduct **4e** as a substrate for skeletal diversity via the Pauson−Khand reaction[15] (PKR) (Scheme 5). The $Co_2(CO)_6$ complex derived from **4e** was consumed

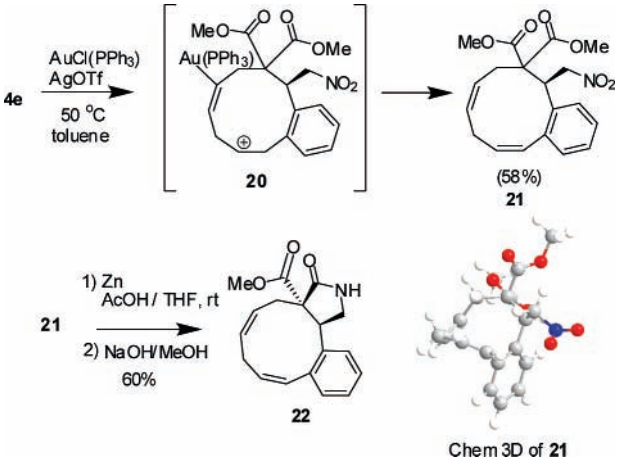
Scheme 5



upon heating to afford a single new product (67%). It was apparent from NMR studies that the structure of the new compound was not the expected fused eight-membered ring **18**. X-ray structure analysis showed that the interesting bridged nine-membered ring **17** had been formed.[16] PKR product **17** is an attractive substrate for diversification through Michael addition as its X-ray structure shows the cyclopentenone group stacked over the aromatic ring allowing access to the enone from one face. An NOE was observed between the vinyl proton of **17** and the methine β to the nitro group demonstrating that the solution phase conformation of **17** was similar to the X-ray structure shown in Scheme 5.[5] When **17** was treated with thiophenol under basic conditions, the Michael adduct **19** was formed with complete selectivity. The expected stereochemistry of **19** was supported by conformational and NOE analyses.[5]

Our emphasis on generating skeletal diversity also led us to investigate cycloisomerization of enyne scaffolds[2b] using homogeneous gold catalysis.[17] Upon thermolysis of **4e** with a cationic gold(I) complex (Scheme 6), a major product was obtained. This product was identified by NMR analysis[5] as the 10-membered cycloisomerization product **21**. The minimum-energy conformer derived from a conformational search (MMFF)[14] of **21** approximates to a chair−boat−chair conformation that is supported by a strong NOE between protons on the two opposite methylene groups in the derived lactam

Scheme 6



22.[5] The stereochemistry of lactam **22** was established by NOE analysis of the corresponding alcohol.[5] Products such as 1,4-diene **21** are unusual in gold(I) chemistry as the normal mode of reactivity generally involves attack of the carbocation by the alkene in **20** to form a cyclopropane intermediate that may rearrange to form a conjugated diene with an exocyclic alkene.[17a] However, in the case at hand, elimination likely competes effectively with cyclopropane formation due to the presence of the aryl ring leading to the observed 10-membered-ring product.

In summary, asymmetric Michael additions of substituted 1,3-dicarbonyls to β-nitrostyrenes employing Cinchona alkaloids have been expanded in scope to prepare a series of acyclic, multifunctional scaffolds. These scaffolds have been utilized in chemical reaction sequences engaging two specific functionalities of interest (functional group pairing) to gain access to a range of five- to ten-membered complex fused and bridged ring systems. The overall approach has also enabled discovery of several interesting reaction types, including an efficient Pauson−Khand cycloaddition leading to a bridged nine-membered ring and a novel Au(I)-catalyzed cycloisomerization to produce a ten-membered ring. Further applications of this strategy as a means to access novel reactions and chemotypes are in progress in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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