Brønsted Base Catalyzed One-Pot Synthesis of Stereodefined Six-Member Carbocycles Featuring Transient Trienolates and a Key Intramolecular 1,6-Addition.

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Abstract: A catalyst-driven one-pot reaction sequence is developed for the enantio- and diastereoselective synthesis of tetrasubstituted cyclohexenes from simple unsaturated ketones or thioesters. The method involves a tertiary amine/squaramide-catalyzed α–selective addition of transiently generated trienolates to nitroolefins, subsequent base-catalyzed double bond isomerization, and an intramolecular (vinylogous) 1,6-addition reaction as yet unreported key carbocyclisation step that proceeded with essentially perfect stereocontrol.

Six-membered carbocycles are ubiquitous structural motifs in natural products and bioactive substances, and their stereoselective synthesis has attracted huge interest. This has traditionally relied on the venerable Diels-Alder reaction, with several metal- and organocatalyzed variants being established already.[1] Catalytic, one-pot domino processes[2] are also valuable approaches, provided that each bond-forming step occurs with high site- and stereofidelity. This is usually achieved by using substrates bearing carefully selected, and strategically positioned, donor and acceptor reaction sites. In this context, covalent aminocatalysis have revealed extremely versatile owing to the complementary donor/acceptor character of the intervening enamine/iminium species, enabling the *de novo* construction of six-membered carbocycles from minimally functionalized aldehyde and ketone substrates.[2,3] Common to these domino processes, the key ring-closing step is achieved through three major approaches: the intramolecular 1,2- and 1,4-addition reactions, the latter in its *endo* and *exo* variants (Figure 1a). It is remarkable that, to the best of our knowledge, no method relying on an intramolecular (vinylogous) 1,6-addition approach[4] has been reported so far, despite such approach would require minimally functionalized substrates. Here we describe a catalytic, enantio- and diastereoselective one-pot construction of six-membered carbocycles that ends up with an unprecedented intramolecular 1,6-addition step. The new method requires Brønsted base catalysts[5] as the only reaction promoter and can equally start from simple unsaturated ketones or (thio)esters (Figure 1b).

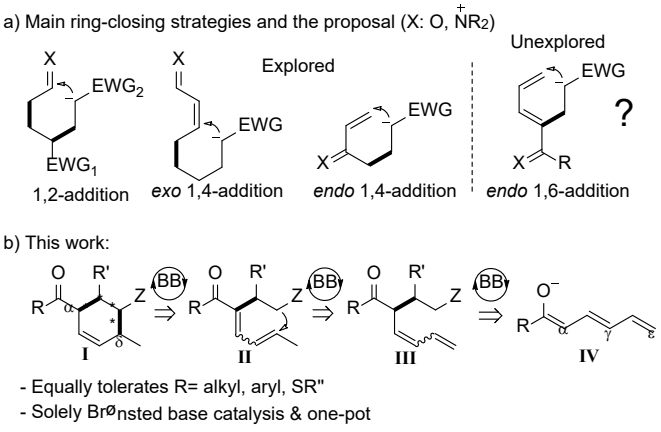

Figure 1. Catalytic one-pot construction of six-membered carbocycles.

In this conception conversion of **III** to **II** seemed conjugation-driven and feasible, but transformations **II**→**I** and **IV**→**III** appeared most difficult and unpredictable. While stereocontrol of **II**→**I** may become an issue,[6] the catalytic Cα-alkylation of transiently generated trienolates **IV** to produce **III** remained unaddressed so far, posing obvious site- and stereoselectivity concerns.[7] Quite recently we have documented.[8] that bifunctional Brønsted base/H-bonding catalysts successfully induce in situ formation of *di*enolates and their α-selective reaction, most likely through an anchoring effect. We hypothesized that the present setting might be a good platform to further proof the generality of the concept. At the outset, the reaction of deconjugated thioester **1A**[9] and nitrostyrene **2a**[10] in dichloromethane in the presence of 10–20 mol% of several amine bases was investigated. As data in Table 1 show, the reaction progressed to essentially full conversion upon 24 hours at room temperature regardless the base used, although product distribution varied considerably. With simple tertiary amine Et_3N, isomerization to the conjugated diene **3A** occurred along with minor formation of α-addition product **4Aa**. With sterically bulkier amine $^{i}Pr_2EtN$, the **4Aa**/**3A** ratio increased notably, but at the expense of diastereoselectivity. The **4Aa**/**3A** product distribution was very similar using chiral, dimeric catalyst $(DHQD)_2PYR$, and the *dr* of product **4Aa** was high (>20:1). Using stronger amine base DBU caused isomerization of substrate to conjugated thioester **3A**. However, in this case cycloadduct **6Aa** was produced for the first time (entry 4), and with essentially perfect diastereoselectivity (*dr* >20:1).[11] We presumed that this cycloadduct might be formed via cyclization of acyclic precursor **5Aa**, followed by double bond isomerization. To proof this

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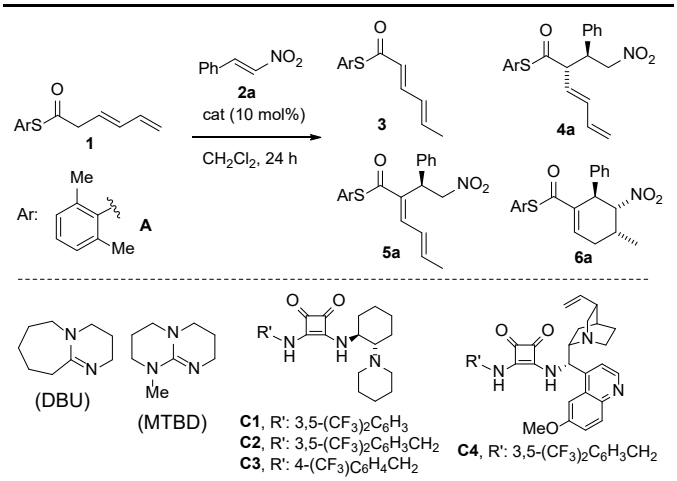
Table 1. Catalyst-dependent product distribution in the reaction of polyunsaturated thioester **1A** with nitrostyrene.[a]



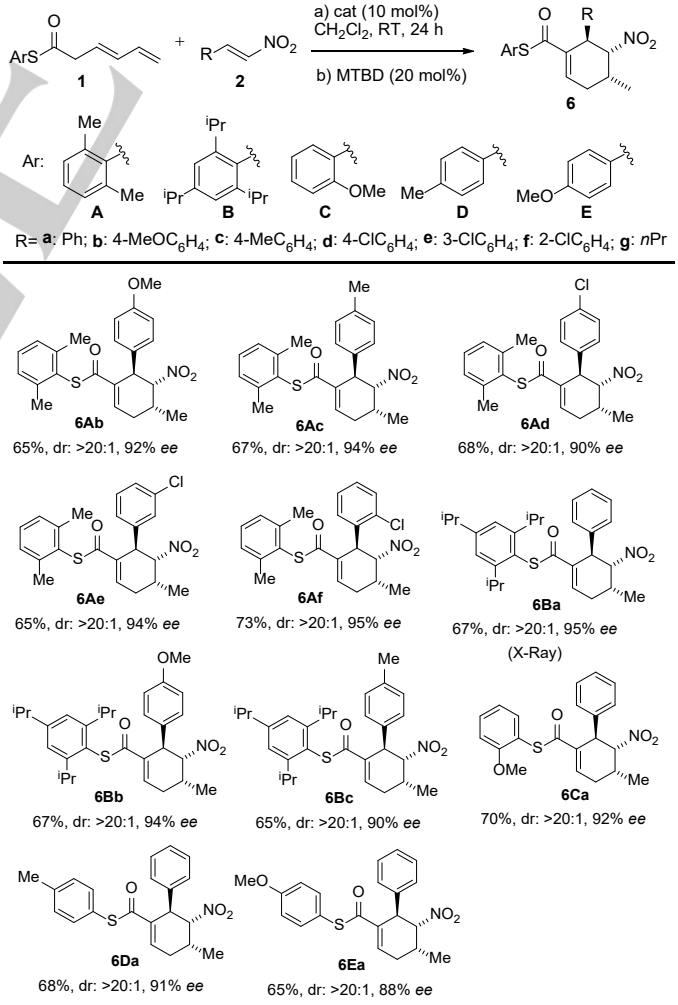
Entry	Cat	3A	4Aa	5Aa	6Aa
1	Et_3N	83	17 (>20:1)	--	--
2	iPr_2EtN	45	55 (1.4:1)	--	--
3	$(DHQD)_2PYR$	45	55 (>20:1)	--	--
4	DBU	70	[b]	--	30 (>20:1)
5	DBU (0 ºC)	58	--	18	24 (>20:1)
6	DBU (0 ºC, 40 h)	58	--	--	42 (>20:1)
7	MTBD (RT, 16 h)	100	--	--	--
8	MTBD (0 ºC, 16 h)	100	--	--	--
9	MTBD (–10 ºC, 16 h)	100	--	--	--
10	**C1**	20	80 (>20:1)	--	--
11	**C1** + MTBD[c]	20	--	--	65[d] (>20:1, 81*ee*)
12	**C2** + MTBD[c]	23	--	--	72[d] (>20:1, 78% *ee*)
13	**C3** + MTBD[c]	25	--	--	
14	**C4 + MTBD**[c]	**18**	--	--	68[d] (>20:1, 88% ee)

[a] Reactions carried out at 0.1 mmol scale, using 1 equiv. of each **1A** and **2a** and 10 mol% catalyst in 0.1 mL CH_2Cl_2 at room temperature. The ratios of products **3A**/**4Aa**/**5Aa**/**6Aa** formed correspond to ^{1}H NMR integration. Data in parenthesis correspond to *d.r.* and *ee*. [b] *ee* not determined. [c] Cocatalyst MTBD (20 mol%) was added after 16 h and stirring kept for additional 24 h.[d] yield after isolation of product by column chromatography. 1.5 equiv. of **1A** were used.

assumption the same reaction was carried out at lower temperature (entry 5, 0 °C) affording a mixture of **3A**, isomerized α-adduct **5Aa**, and **6Aa**. When this mixture was allowed to stir for longer time at 0 °C, a mixture of **3A** (58%) and **6Aa** (42%) was isolated (entry 6), indicating that indeed **5Aa** is an intermediate in the formation of **6Aa**. The use of even stronger guanidine base MTBD was disappointing, as isomerized thioester **3** was the only isolated product regardless the reaction temperature (entries 7-9). It thus seems that conjugated thioester **3A** is a thermodynamic sink. Then, with the hope to ease the C–C bond forming event by simultaneous activation of the electrophile, bifunctional Brønsted base/H-bonding catalysts were investigated. Gratifyingly, the reaction carried out in the presence of squaramide **C1**[12] led to α-addition adduct **4Aa** with the highest isolated yield so far (80%) along with 20% of isomerized material **3A** (entry 10). When this mixture was stirred for an additional 20 h in the presence of 20 mol% DBU or MTBD, total conversion of **4Aa** into the cyclisation product **6Aa** was observed, the latter obtained in 65% isolated yield as essentially pure diastereomer and most significantly in 81% *ee* (entry 11). For this one-pot two-step transformation,[13] the structurally related amine-squaramide catalysts **C2** and **C3** resulted equally effective, affording single diastereomer cycloadduct **6Aa** in yields of 72% and 68% and *ee*'s of 78% and 88%, respectively (entries 12, 13). Finally, the quinine-derived catalyst **C4** led to improved 94% *ee* (entry 14).

Several thioesthers **1**, with variable aryl groups at sulfur, and nitroalkenes **2** were subjected to the optimized conditions, consisting of, first, stirring the mixture in the presence of 10 mol% **C4** and, second, one-pot treatment with 20 mol% of either DBU or MTBD. As the results in Table 2 show, the reaction with nitrostyrenes bearing electron-reach MeO and Me *p*-substituents (adducts **6Ab**, **6Ac**) or electron-poor *p*-substituent Cl (adduct **6Ad**) all proceeded with good yields, perfect regio- and diastereoselectivity and enantioselectivity of 90% *ee* or higher.

Table 2. Catalytic enantioselective reaction of thioesters **1** with nitroolefins to afford tetrasubstituted cyclohexenes **6**.[a]



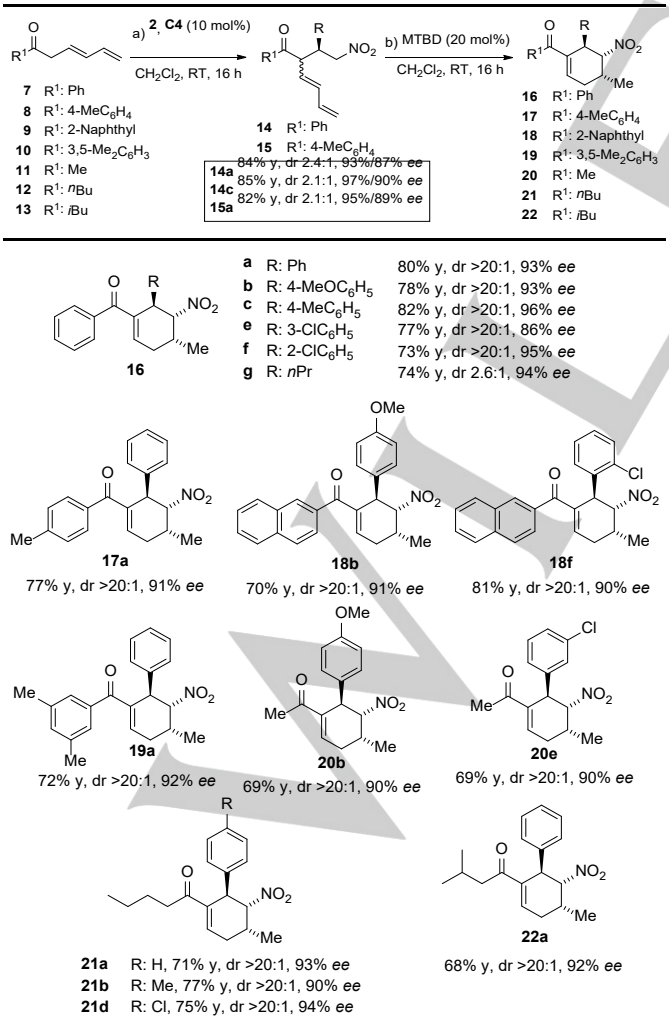
[a] Reactions carried out at 0.1 mmol scale, using 1.5 equiv. of **1** and 10 mol% catalyst in 0.1 mL DCM at room temperature. Variable amounts (~20%) of isomerized starting material were observed in most entries [b] Yield after chromatography. [c] Determined by ^{1}H NMR (300 MHz). [d] *ee*

determined by chiral HPLC.

The position of substitution neither affected the reaction efficiency as the good yields and high selectivities obtained with the *m*- and *o*-substituted nitrostyrenes **2e** and **2f** show (adducts **6Ae** and **6Af**). With respect to variation in the thioester group, thioesters with *o*-*p* triisopropyl substituted phenyl groups (products **6B**) worked equally well, as did thioesters with only *o*- or only *p*-substituted phenyls (adducts **6C**–**6E**).

The scope of this new design approach to cyclohexenes was next examined from deconjugated dienones **7**–**13** which, as far as we are aware, have neither been studied under Brønsted base/H-bonding catalysis conditions. As shown in Table 3, the reaction of unsaturated ketone **7** with nitrostyrene **2a** in the presence of 10 mol% catalyst **C4** cleanly afforded α-addition adduct **14a** in 74%

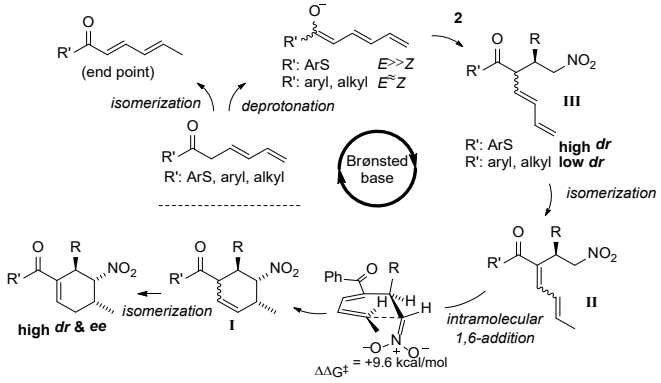
Table 3. Catalytic enantioselective one-pot two-step synthesis of tetrasubstituted cyclohexenes from ketone trienolates and nitroolefins.[a]



[a] Reactions carried out at 0.1 mmol scale, using 1.2 equiv. of **7**–**13** and in 0.1 mL DCM at room temperature. Yield after chromatography. Dr are determined by ^{1}H NMR (300 MHz). *Ee* are determined by chiral HPLC.

yield as a 2.4:1 mixture of diastereomers in 93% and 87% *ee*, respectively. The regio- and stereochemical outcome of this catalytic reaction appears to be independent of the nature of the nitroolefin and/or starting ketone used, as the results with nitroolefin **2c** (adduct **14c** 85% yield, 2.1:1 dr and 97%/90% *ee*) and *p*-tolyl ketone **8** (adduct **15a**, 82% yield, 2.1.1 dr and 95%/89% *ee*) illustrate.[14] Interestingly, the smooth base-promoted intramolecular cyclization of thus formed adducts afforded in all the cases studied cyclohexenes **16**-**22** in a highly diastereoselective manner. For instance, phenyl ketone **7** upon reaction with nitrostyrenes **2a**–**2f** provided adducts **16a**–**f** with isolated yields in the range 73-82%, diastereomeric ratios >20:1, and enantioselectivity typically higher than 90%. The reaction with the aliphatic nitroalkene **2g** did also proceed efficiently to give **16g**, but in this instance a 2.6:1 mixture of diastereomers was formed. Other unsaturated enolizable ketones with aryl (**8**, **9**, **10**) or alkyl (**11**, **12**, **13**) side chains were also tolerated, affording the corresponding adducts **17**–**22** in good yields and high stereoselectivity. These results overall make clear that the high enantio- and regiocontrol imparted by bifunctional Brønsted base catalysts during trienolates functionalization are instrumental. Previously established technology using similar polyunsaturated substrates, i.e. trienamine-mediated activation, becomes unsuitable due to its inability to activate (thio)esters and/or divergent reactivity patterns.[3h, 15]

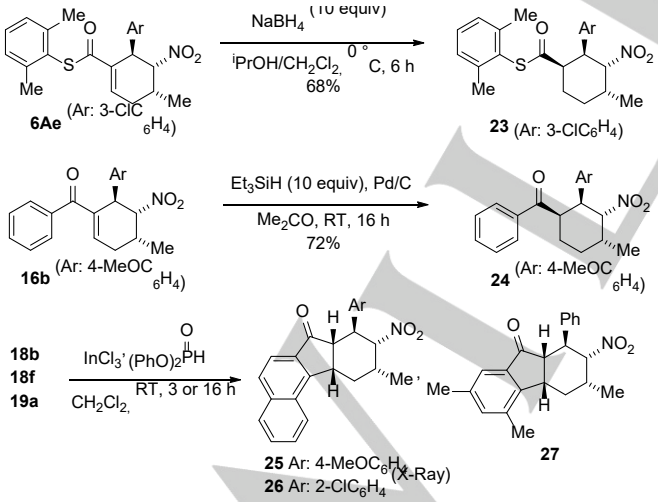
The above results reinforce the hypothesis that cycloadducts are formed through an intramolecular 1,6-addition[16] occurring in the isomerized dienone **II** (Figure 1). Thus, the low selectivity at Cα in the initially formed adducts **III**, such as **14** and **15**, is irrelevant. To support this assumption and the almost perfect stereocontrol (with the exception of **16g**), the energies of the TS for the carbocyclization step in its four possible nitronate-dienone face combinations were calculated. The energy barrier for the *re*,*re* approach was found to be 9.6 kcal/mol (Scheme 1), that is, about 2 kcal/mol lower than any of the other three possible approaches (see the SI for details), in good agreement with the high diastereocontrol observed. According to the data at hand, a plausible scheme of events is depicted in Scheme 1, in which Brønsted base catalysis would be the unified activation mechanism. In that full picture, the low diastereoselectivies observed for the initial α-addition reaction of doubly unsaturated ketones to nitroolefins could be ascribed to their tendency to form variable mixtures of *E* and *Z* enolates.



Scheme 1. Plausible course of the one-pot reactions sequence.

Conversely, the high diastereoselectivity attained with unsaturated thioesters would correlate with the relatively higher energy difference between thioester *Z* and *E* enolate, owing to the large arylthio group. The relative and absolute configuration of compound **6Ba** was determined by X-ray single crystal structure analysis[17] and that of the remaining adducts was assumed based on a uniform reaction mechanism.

Several transformations of these polysubstituted cyclohexene adducts were explored (Scheme 2). Selective reduction of the C–C double bond in thioester **6Af** was achieved by simply using an excess of $NaBH_4$ in isopropyl alcohol and CH_2Cl_2 mixture, affording cyclohexane **23** as the only isomer in 68% isolated yield. In its turn, the reduction of enone **16b** to **24** could be achieved in 72% yield and without affecting the carbonyl group by using Et_3SiH in the presence of Pd/C.[18] Interestingly, these cyclohexene adducts also resulted well suited for expanding the Nazarov cyclisation,[19] as demonstrated by the conversion of adducts **18b**, **18f** and **19a** into products **25**-**27** in good yields and as essentially single diastereomer. The structure of these polycyclic products were established by NMR experiments and corroborated by X-ray analysis of **26**.[17]



Scheme 2. Elaboration of adducts through reduction and Nazarov cyclisation.

In summary, a catalytic one-pot process to assemble stereodefined tetrasubstituted six membered carbocycles from polyunsaturated thioesthers or ketones is developed. The new method features: (i) a highly enantioselective α-addition of transiently generated trienolates to nitrolefins, (ii) an intramolecular 1,6-addition as previously unreported carbocyclisation approach, which proceeded with essentially perfect stereocontrol, and (iii) two intermediate C=C isomerization processes, with Brønsted base catalysts as the only promoters. Importantly, the α-addition pathway observed for trienolates is divergent from the [4+2] cycloaddition pathways dominant in trienamine mediated chemistry,[3h, 15] and provides a route to complementary cyclohexene systems. Given that both proton transfer and H-bonding are general activation modes, new enantioselective reactions involving trienolate-like π-extended systems from carbonyl and non-carbonyl substrates might be predictable.

Acknowledgements

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Keywords: Brønsted bases • 1,6-conjugate additions • organocatalysis • trienolates • synthetic methods

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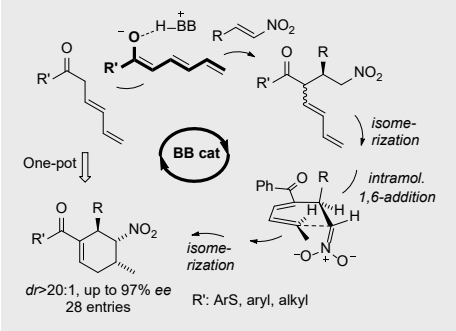
Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

Consecutive BB catalysis: Brønsted base catalysis is able to concatenate a sequence of events including trienolate formation, it's α-addition to nitroolefins, and a key intramolecular 1,6-addition, with two intermediate C=C isomerizations, stereoselectiviely to end up with the one-pot assembly of tetrasubstituted cyclohexenes



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Brønsted Base Catalyzed One-Pot Synthesis of Stereodefined Six-Member Carbocycles Featuring Transient Trienolates and a Key Intramolecular 1,6-Addition