EDGE ARTICLE

Nitro-enabled catalytic enantioselective formal *umpolung* alkenylation of β-ketoesters†

Abhijnan Ray Choudhury, ‡ Madhu Sudan Manna ‡ and Santanu Mukherjee *

A formal *umpolung* strategy is presented for the enantioselective installation of an alkenyl group with a terminal double bond at a tertiary center. This one-pot two-step sequence relies on the unique features of the nitro group, which after inverting the polarity of the alkenylating agent toward the desired bond formation, itself serves as a leaving group. The application of this protocol to cyclic β-ketoesters results in densely functionalized products, bearing an all-carbon quaternary stereocenter including an alkenyl substituent with a terminal double bond, in high yields with excellent enantioselectivities.

Introduction

An all-carbon quaternary stereogenic center bearing an alkenyl substituent is a structural motif found in various families of natural products and bioactive molecules (Fig. 1).[1] While enantioselective construction of all-carbon quaternary stereocenters is itself considered challenging,[2] those bearing an alkenyl substituent present an additional level of difficulty due to the lack of available synthetic methods for the installation of alkenyl groups at sterically hindered positions.

Driven by these challenges, the past decade has witnessed the emergence of a number of strategies for the catalytic enantioselective α-alkenylation of carbonyl and related compounds.[3–5] However, the majority of these reactions lead to the products bearing the alkenyl group with an internal double bond (Scheme 1A).[3,4] In contrast, enantioselective installation of an alkenyl group with a terminal double bond is far less explored[5] and calls for innovative strategies.

In an effort to address this issue, we contemplated the development of a catalytic enantioselective α-alkenylation of β-ketoesters[6] – a reaction which would furnish a product bearing an all-carbon quaternary stereogenic center. The conventional
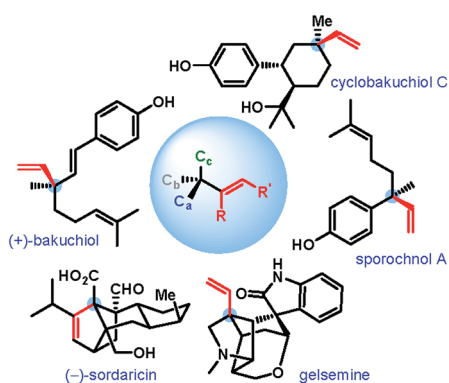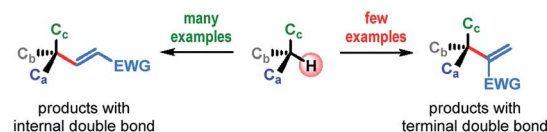

Fig. 1 Natural products with alkenyl-bearing all-carbon quaternary stereocenters.

Department Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India. E-mail: sm@orgchem.iisc.ernet.in; Fax: +91-80-2360-0529; Tel: +91-80-2293-2850
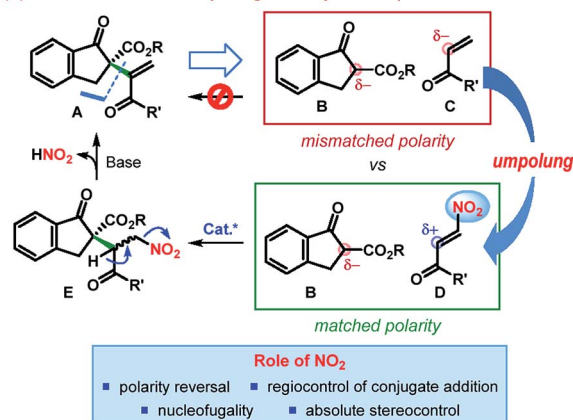
‡ These authors contributed equally to this work.

Scheme 1 Enantioselective construction of alkenyl-containing all-carbon quaternary stereocenters.

retrosynthetic analysis of a potential product of type **A**, bearing an alkenyl group with a terminal double bond, leads to a pair of synthons (**B** & **C**) having "mismatched polarity", thereby making such a process electronically improbable (Scheme 1B). Consequently, polarity reversal (*umpolung*)[7] of one of these synthons would be essential to effect this C–C bond formation.

Recent investigations by our laboratory and others have established the nitro functional group as a powerful directing as well as leaving group.[8] We reasoned that appending enone **C** with a nitro group at its β-position would reverse its naturally nucleophilic α-position to an electrophilic center (Scheme 1B). The desired C–C bond formation between the resulting β-nitroenone **D** and the β-ketoester **B** would then be electronically feasible ("matched polarity"). In fact, owing to the hydrogen bonding acceptor ability of the nitro group, the conjugate addition could be catalyzed regioselectively with the use of a suitable H-bond donor. Control of the stereochemistry (by the catalyst) at the prochiral center would lead, in the worst case, to an inconsequential mixture of diastereomers (**E**). Nucleofugality of the nitro group along with the presence of a suitably placed acidic proton in **E** should eventually facilitate the elimination of nitrous acid, leaving behind an all-carbon quaternary stereogenic center bearing an alkenyl group with a terminal double bond. Apart from the nucleofugality of the nitro group, this strategy is built on the ability of the nitro group to invert the natural polarity of enone (*umpolung*) as well as to control the regio- and stereoselectivity of the conjugate addition.[9]

Results and discussion

To ascertain the viability of our postulated formal *umpolung* alkenylation reaction, we began our study with a β-ketoester derived from 1-indanone (**1**) as the pronucleophile and phenyl β-nitroenone **2a** as the alkenylating agent (Table 1). Based on their proven efficacy in enantioselective transformations of nitro compounds, tertiary amino-(thio)urea derivatives were selected as the potential catalyst candidates.[10] Initial screening of ester substituents on **1** revealed the *t*-Bu group to be optimal, with respect to the diastereoselectivity of the initial conjugate addition step.[11] However, irrespective of the ester substituent, Michael addition was found to take place with exquisite regioselectivity to furnish **3** as the sole product. The optimization of the catalyst and reaction conditions was then undertaken for the reaction between *tert*-butyl β-ketoester **1a** and **2a**. The undesired background reaction operating at 25 °C (entry 1) was eliminated by conducting the reaction at −60 °C (entry 2). Solvent screening with dihydroquinine-derived thiourea **I** as the catalyst established 2-MeTHF as the preferred reaction medium.[11] Under these conditions, the Michael adduct **3aa** was formed in 88% yield with >20 : 1 dr. (entry 3). As anticipated, treatment of **3aa** with DBU in THF at ambient temperature resulted in the desired α-alkenylation product **4aa**, bearing an all-carbon quaternary stereocenter, in 85% yield with 94.5 : 5.5 er. The related (thio)urea derivatives **II–V** failed to improve the enantioselectivity (entries 4–7). Replacing the 3,5-bis(tri-fluoromethyl)phenyl group of thiourea in **I** with 3,5-

Table 1 Catalyst identification and optimization of reaction conditions[a]

Entry	Catalyst	t [h]	Yield [%] of **3aa** [b]	Yield [%] of **4aa** [b]	er of **4aa** [c]
1[d]	None	6	90	90	—
2	None	48	<5	—	—
3	**I**	48	88	85	94.5 : 5.5
4	**II**	46	95	87	94 : 6
5	**III**	48	>99	86	92 : 8
6	**IV**	48	90	86	92 : 8
7	**V**	48	90	85	93 : 7
8	**VI**	48	>99	88	70 : 30
9	**VII**	24	>99	88	97.5 : 2.5
10[e,f]	**VII**	24	—	48	97.5 : 2.5
11[e,g]	**VII**	24	—	91	97.5 : 2.5

[a] Reactions were carried out on a 0.1 mmol scale using 1.0 equiv. of **1a** and 1.2 equiv. of **2a**. [b] Yields correspond to the isolated product. [c] The enantiomeric ratio (er) was determined by HPLC analysis. [d] Reaction at 25 °C. [e] Using 2.0 equiv. of DBU. [f] One-pot reaction in 2-MeTHF. Time required for the 2nd step was 40 h. [g] One-pot reaction with solvent switch.

bis(trifluoromethyl)benzyl resulted in a poorly enantioselective catalyst **VI** (entry 8). However, catalyst **VII** containing a cyclohexyl moiety was found not only to be more active, but also furnished the product **4aa** with excellent er (entry 9). The elimination step was found to be considerably slower when conducting the two steps in a one-pot manner in 2-MeTHF (entry 10), although it did not influence the enantioselectivity. Finally, a solvent switch (to THF) prior to elimination proved beneficial and provided **4aa** with improved yield and identical er (entry 11). Attempts to further improve the enantioselectivity through additives or by tweaking other reaction parameters proved futile.[11]

Table 2 summarizes the scope and limitations of this catalytic enantioselective formal *umpolung* alkenylation protocol under the optimized catalyst and reaction conditions (Table 1, entry 11). Our protocol was found to be operational with a variety of electronically tuned and sterically diverse β-nitroenones **2** (Table 2A). Different *para*- and *meta*-substituted aryl β-nitroenones (**2b–h**) could be employed to generate the desired

Table 2 Scope of the catalytic enantioselective formal *umpolung* alkenylation of β-ketoesters[a]

(A)

Entry	R[1]	t [h]	Yield [%]	er
1	Ph (4aa)	24	91	97.5 : 2.5
2	4-MeC_6H_4 (4ab)	24	90	97 : 3
3	4-MeOC_6H_4 (4ac)	24	82	97 : 3
4	4-ClC_6H_4 (4ad)	24	86	98 : 2
5	4-FC_6H_4 (4ae)	24	87	98 : 2
6	3-MeOC_6H_4 (4af)	24	87	97 : 3
7	3-MeC_6H_4 (4ag)	24	82	97 : 3
8	3-ClC_6H_4 (4ah)	24	81	96.5 : 3.5
9	2-MeC_6H_4 (4ai)	36	80	97.5 : 2.5
10	2-MeOC_6H_4 (4aj)	36	87	98.5 : 1.5
11	1-naphthyl (4ak)	36	78	98 : 2
12	2-naphthyl (4al)	36	90	97 : 3
13	2-thienyl (4am)	48	79	98.5 : 1.5
14	2,4-(MeO)_2C_6H_3 (4an)	48	76	94.5 : 5.5
15	(4ao)	40	89	95 : 5
16	(4ap)	72	57	97.5 : 2.5

(B)

Entry	R	t [h]	Yield [%]	er
1	Br (4ba)	24	93	98 : 2 (>99.9 : 0.1)[b]
2	Cl (4ca)	24	93	98 : 2 (>99.9 : 0.1)[b]
3	F (4da)	24	95	98 : 2
4	Me (4ea)	24	82	98 : 2
5	Ph (4fa)	30	75	98 : 2

(C)

Entry	R	t [h]	Yield [%]	er
1	Br (4ga)	24	91	99 : 1
2	Me (4ha)	24	96	98.5 : 1.5
3	OMe (4ia)	24	92	97.5 : 2.5

(D)

4ja
24 h, 95% yield
96.5:3.5 er

4ka
30 h, 90% yield
96.5:3.5 er

4bd
36 h, 86% yield
99:1 er

4la
40 h, 87% yield
97.5:2.5 er

4ma
48 h, 65% yield
90:10 er

4ba
(CCDC 1491357)

[a] Yields correspond to the isolated yield. er determined by HPLC analysis using a stationary phase chiral column. [b] Values in parentheses correspond to the er after a single recrystallization.

alkenylated products **4ab–ah** in high yields with excellent enantioselectivities (entries 2–8). Controlling the enantioselectivity of the reactions involving *ortho*-substituted aromatic substrates is generally a cause of concern in asymmetric synthesis. We were delighted to find our protocol to be equally suited for *ortho*-substituted aryl β-nitroenones (**2i–j**) as the products (**4ai–aj**) were formed with excellent enantioselectivities

(entries 9–10). The same trend was observed for the products (**4ak–ao**) derived from β-nitroenones bearing naphthyl (**2k–l**), 2-thienyl (**2m**) and highly electron rich aryl substituents (**2n–o**) (entries 11–15). An excellent er prevailed even in the case of an alkyl-substituted β-nitroenone, although the product **4ap** was obtained only with modest yield (entry 16). The formation of an internal olefin (in 22% yield) accounts for the diminished yield in this case.[11]

The scope of *tert*-butyl β-ketoesters with respect to the substituents on the aryl ring was also tested. As illustrated in Table 2B, various 5-substituted 1-indanone derived β-ketoesters (**1b–f**) were found to be suitable substrates and the products **4ba–fa** were obtained generally in high yields with excellent enantioselectivities. Please note that the alkenylated products **4ba** and **4ca** could be obtained essentially in enantiopure form after a single recrystallization. Similarly, 6-substituted 1-indanone derived β-ketoesters (**1g–i**) resulted in the products **4ga–ia** with superb er (Table 2C). Substituents on the 4- and 7-positions of 1-indanone, too, were tolerated and furnished the products **4ja** and **4ka**, respectively, in high yields and enantioselectivities (Table 2D). In fact, *tert*-butyl β-ketoesters derived from cyclopentenones (**1l–m**) were also found to be competent substrates and the desired products **4la–ma** were obtained in high yields with good to excellent enantioselectivities. However, β-ketoesters derived from larger ring ketones (*e.g.* 1-tetralone and 1-benzosuberone) and acyclic ketones were found to be completely unreactive under our optimized reaction conditions,[11] and hence mark the present limitation of our protocol.

To rule out the possibility of enantioenrichment of the products through self-disproportionation of enantiomers (SDE),[12] we performed a SDE test through achiral chromatography on silica gel. No noticeable enantioenrichment/depletion was observed in this process, thereby confirming that the enantiomeric ratios reported in Tables 1 and 2 are a direct outcome of the catalytic reactions.

Single crystal X-ray diffraction analysis of the alkenylated product **4ba** (Table 2D) enabled us to establish its absolute configuration, which was found to be (S).[13] The configurations of the other products, shown in Table 2, were tentatively assigned by analogy as the same, assuming a similar catalytic mechanism was followed.

To demonstrate the scalability of our protocol, a reaction between *tert*-butyl β-ketoester **1a** and phenyl β-nitroenone **2a** was carried out on a 1.0 mmol scale with only 5 mol% of catalyst **VII** (Scheme 2). Albeit with a longer reaction time, **4aa** was obtained in nearly quantitative yield with the same level of enantioselectivity as that obtained with the small scale reaction. Moreover, catalyst recovery was possible with 77% yield.

The utility of the products obtained through the enantioselective formal *umpolung* alkenylation reaction was displayed through a few synthetic modifications. For example, hydrogenation of **4aa** under Pd-catalysis led to the reduction of the alkene and furnished **5** as a single diastereomer in 68% yield (Scheme 2). Chemo- and diastereoselective reduction of the cyclic ketone in **4aa** over the enone functionality was achieved
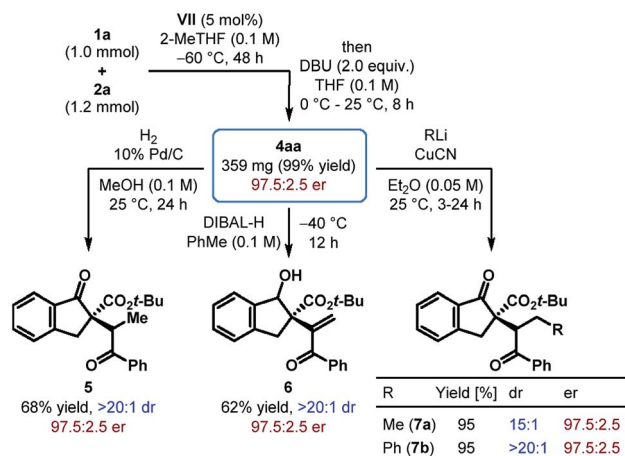
Scheme 2 Scalability of the reaction and synthetic elaboration of the alkenylation product.

with DIBAL-H and the alcohol **6** was formed in 62% yield. The Cu(I)-mediated addition of organolithium reagents to **4aa** proceeded regioselectively in a 1,4-fashion and the resulting products **7a–b** were generated in excellent yields with good to outstanding dr. In all these reactions, the products were obtained without compromising the stereochemical integrity of the starting material.

Conclusions

In conclusion, the intricate task of installing an alkenyl group with a terminal double bond enantioselectively at a tertiary center has been accomplished through the reaction between two seemingly polarity mismatched coupling partners. The result is a highly efficient and enantioselective formal *umpolung* α-alkenylation of cyclic β-ketoesters. This reaction proceeds through a one-pot two-step sequence consisting of a catalytic regio-, diastereo- and enantioselective conjugate addition to β-nitroenones followed by a base mediated nitrous acid elimination. Catalyzed by a dihydroquinine-based bifunctional tertiary aminothiourea derivative, this process delivers synthetically versatile products bearing an all-carbon quaternary stereocenter including an alkenyl substituent with a terminal double bond in high yields with excellent enantioselectivities. We expect this alkenylation strategy to be applicable to other classes of substrate as well. These possibilities are currently under investigation in our laboratory.

Acknowledgements

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