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A torquoselective extrusion of isoxazoline *N*-oxides. Application to the synthesis of aryl vinyl and divinyl ketones for Nazarov cyclization

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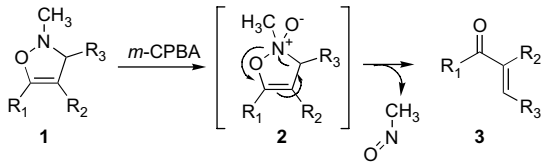
ABSTRACT

A mild, convenient reaction sequence for the synthesis of Nazarov cyclization substrates is described. The [3+2] dipolar cycloaddition of a nitrone and an electron-deficient alkyne gives an isolable isoxazoline intermediate, which upon oxidation undergoes stereoselective extrusion of nitrosomethane to give aryl vinyl or divinyl ketones.

1. Introduction

One of the most important factors determining synthetic utility of Nazarov cyclization is the efficiency of divinyl ketone preparation. A number of specific methods have been developed for their synthesis, depending on the vinyl substitution pattern desired.[1–5] For the preparation of substrates with electron-withdrawing groups such as those employed in Lewis acid-catalyzed Nazarov cyclizations of polarized substrates,[6] Knoevenagel condensation has been the only option.[7] Disadvantages of the procedure include: the requirement for a β-ketoester precursor, which can be quite difficult to prepare efficiently; reaction conditions involving high temperatures; long reaction times; and either acidic or basic pH, all of which can destroy sensitive functionality. Because the condensation is thermodynamically controlled, mixtures of diastereomers are obtained. Finally, it can be difficult to prevent the divinyl ketone from undergoing premature Nazarov cyclization during acid-catalyzed Knoevenagel condensation.

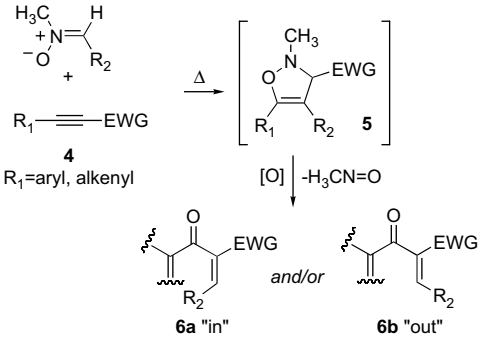
An unusual reaction was reported by Padwa in 1987, in which Δ^4-isoxazolines **1** underwent oxidative extrusion of nitrosomethane to give α-β-unsaturated ketones **3** (Scheme 1).[8]



Scheme 1. Padwa's oxidation of Δ^4-isoxazolines.

Upon treatment with *m*-CPBA, the ring nitrogen of isoxazoline **1** is thought to undergo oxidation to give intermediate **2**, which cannot be isolated or even observed by NMR spectroscopy. Instead, immediate extrusion of nitrosomethane from putative *N*-oxide **2** occurs at low temperature to give **3** with surprisingly high stereoselectivity. The yields were good in the reported cases, although the scope was limited. This sequence provided us with a useful starting point to solve the problems associated with the preparation of Nazarov substrates.

This paper describes a mild and versatile [3+2] cycloaddition/nitrosomethane extrusion process for the synthesis of divinyl ketones for Nazarov cyclization. The reaction sequence is shown in Scheme 2: cycloaddition of a nitrone and an electron-deficient alkyne gives a stable isoxazoline **5** (see Scheme 1). Oxidation leads to extrusion of nitrosomethane at low temperature to give a Nazarov precursor of type **6**.



Scheme 2. [3+2]/[O] sequence for synthesis of Nazarov substrates.

The reaction sequence has not only proven to be an efficient and stereoselective method for the synthesis of Nazarov cyclization

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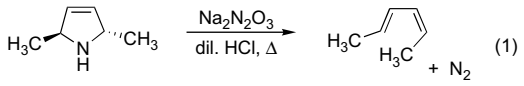
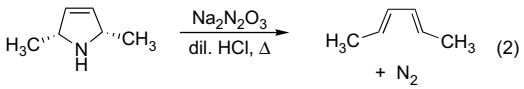
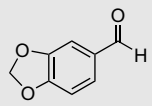
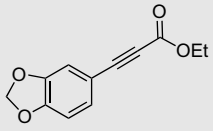
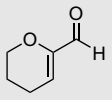
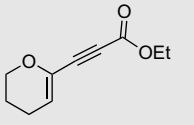
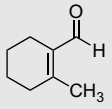
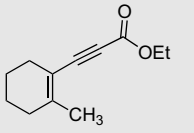
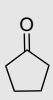
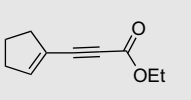
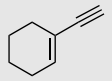
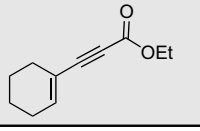
precursors, but the unexpected stereoselectivities observed have also raised interesting questions about the factors controlling the 'cheletropic' fragmentation of oxidized isoxazolines like **2**. Cheletropic extrusions are a class of retro-cycloaddition reactions in which two sigma bonds flanking a single atom of a ring system are broken during a concerted bond reorganization.[9] Two examples of cheletropic extrusions of $(4n+2)$ systems that give stereochemistry consistent with Woodward–Hoffmann theory are shown in Eqs. 1 and 2.





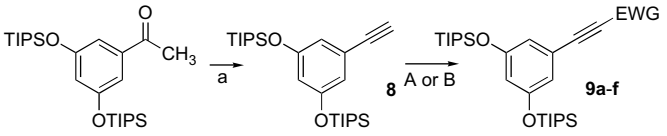
Extrusion can occur in either an *inward* or an *outward* direction,[10] and for unsymmetric substrates two diastereomeric products can be obtained. If one of these senses of rotation is favored over the other, the reaction is termed 'torquoselective,' as defined by Houk. Typically, the sense of rotation is controlled by stereoelectronic effects rather than steric effects, and the stereochemical outcome of many torquoselective reactions, including Nazarov cyclizations, sigmatropic shifts, electrocyclic ring openings and closures, and the Cope rearrangement, [11,12] can be predicted using Houk's theoretical model.[11] An alternative theory, proposing a role for geminal bonds in the torquoselectivity of retro-electrocyclizations, has also been proposed.[11f,13] As will be discussed, the stereochemistry observed in the oxidation/extrusion sequences could not be rationalized using conventional methods, but computational studies led to new mechanistic proposals to explain the torquoselective extrusion.

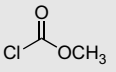
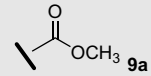
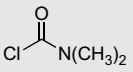
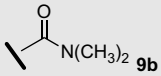
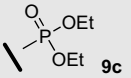
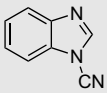
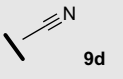
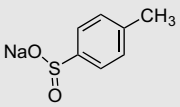
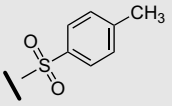
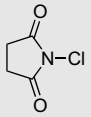
Table 1
Preparation of alkynoates

Entry	Substrate	Conditions	Product	Yield (%)
1		**7a** A		**4a** 89
2		**7b** A		**4b** 63
3		**7c** A		**4c** 78
4		**7d** B		**4d** 58
5		**7e** C		**4e** 95

Reaction conditions: (A) 1. CBr_4, PPh_3, CH_2Cl_2; 2. *n*-BuLi, ClC(O)OEt, THF, −78 °C. (B) LiCC–C(O)OEt, THF, −78 °C; 2. $POCl_3$, pyridine, 90 °C. (C) *n*-BuLi, ClC(O)OEt, THF, −78 °C.

Table 2
Synthesis of alkynes bearing different electron-withdrawing groups



Entry	Electrophile	Conditions	Product	Yield (%)
1		A	 **9a**	98
2		A	 **9b**	77
3		A	 **9c**	95
4		A	 **9d**	74
5		B	 **9e**	83
6		A	–Cl **9f**	61

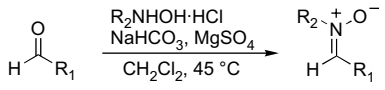
Reaction conditions: (a) *i*. LDA, THF, −78 °C; *ii*. $ClP(O)(OEt)_2$, −78 to 23 °C; *iii*. LDA, THF, −78 to 23 °C. (A) *n*-BuLi, electrophile, THF, −78 °C. (B) *i*. CAN, NaI, *p*-tolSO_2Na, CH_3CN; *ii*. K_2CO_3, acetone, Δ.

2. Results

A majority of the acetylenic esters were prepared from the corresponding aldehydes via Corey–Fuchs[14] protocol, followed by acylation of the resulting alkyne (Table 1). Ester **4a**[15] was made from commercially available piperonal **7a**, in 89% overall yield (entry 1). Pyranyl ester **4b** was readily prepared from pyranyl aldehyde **7b**[16] in 63% overall yield (entry 2). Known methyl substituted cyclohexenyl aldehyde **7c**[17] gave methylcyclohexenyl ester **4c** in 78% yield over two steps (entry 3). Cyclopentenyl ester **4d** was prepared by the addition of lithiated ethyl propiolate to commercially available cyclopentanone **7d**, followed by dehydration with $POCl_3$ in pyridine, to give 58% yield over two steps (entry 4). Cyclohexenyl ester **4e** was obtained by acylation of enyne **7e**[18] with ethyl chloroformate in 95% yield (entry 5).

A series of substrates were prepared from the terminal alkyne **8**, which was obtained from the methyl ketone by a three-step one-pot reaction sequence (Table 2).[19] Deprotonation of alkyne **8** followed by addition of a range of electrophiles provided **9a–f** in good overall yields. *N*-Cyanobenzotriazole was selected as a cyanating reagent to prepare **9d**. Sulfone **9e** was synthesized by reacting

Table 3
Preparation of nitrones



Entry	R^1	R^2	Yield (%)
1	Phenyl	Me	**10a** (84)
2	Cyclohexyl	Me	**10b** (89)
3	*trans*-Cinnamyl	Me	**10c** (82)
4	*trans*-α-Methylcinnamyl	Me	**10d** (89)
5	2,4,6-Trimethoxyphenyl	Me	**10e** (83)
6	3,4,5-Trimethoxyphenyl	Me	**10f** (89)
7	Triethylphenyl	Me	**10g** (25)
8	Phenyl	*t*-Bu	**10h** (69)
9	Cyclohexyl	*t*-Bu	**10i** (73)
10	*trans*-Cinnamyl	*t*-Bu	**10j** (75)

alkyne **8** with sodium *p*-toluenesulfinate in the presence of ceric ammonium nitrate and sodium iodide, followed by base-induced elimination of H–I to recover the alkyne **9e**.[20] Haloalkyne **9f** was easily synthesized by deprotonation of terminal alkyne **8** followed by addition of *N*-chlorosuccinimide. These alkynyl substrates could be prepared on multigram scale with no complications.

Nitrones can be prepared in a variety of ways, most commonly by condensation of carbonyl compounds with *N*-alkyl hydroxylamines.[21] The condensations are typically run in the presence of either an acid scavenger or a water scavenger. We obtained the best results when both an acid scavenger and $MgSO_4$ in refluxing methylene chloride were used (Table 3). In this way it was possible to prepare aryl, alkyl, and conjugated nitrones **10a**–**g** (entries 1–7). Additional nitrones bearing a different substituent on the nitrogen were prepared using *tert*-butyl hydroxyl amine giving nitrones **10h**–**j** (entries 8–10).

With an array of alkynes and nitrones in hand, we applied the cyclization/oxidation reaction sequence to obtain dienones (Table 4). The [3+2] cycloaddition of alkynoates and nitrones proceeded without complication to provide isoxazolines, which were either isolated in good yield, or carried directly to the next step without purification. Oxidation was carried out using *m*-CPBA, generating trisubstituted olefins via extrusion of nitrosomethane at low temperature and in high yield. The resulting olefin geometry is denoted as 'in' or 'out' depending on the stereochemistry of the olefin substituent relative to the alkyl or aryl substituent that is installed from the alkyne starting material. Identification of stereoisomers was assigned by analysis of $^3J_{C,H}$ coupling constants.[22] It was found that for most substrates, the extrusion was highly stereoselective, favoring one olefin diastereoisomer. In most cases, the substituent R^2 emerged cis to the ketone to give 'in' stereoisomers in >15:1 selectivity (entries 1, 7, and 8). However, in a few cases the 'out' stereoisomeric product, in which R^2 is cis to the ester, was dominant (entries 2 and 4). When the ester substitution was changed from ethyl (entry 5) to *tert*-butyl (entry 6), the product mixture showed decreased selectivity for the 'in' isomer.

We next investigated this reaction sequence using piperonal derived alkyne **4a** and nitrones that contained aryl groups with varying steric bulk and electronics (Table 5). Using an unsubstituted phenyl ring on the nitrone, the major product after oxidative extrusion was the 'in' stereoisomer in a ratio of >15:1 (entry 1). When the alkynyl ester **4a** was replaced with an analogous *tert*-butyl ester, the same stereoisomer was favored, and the ratio dropped to 8:1 (entry 2) as we had observed in Table 1 (entries 5 and 6). By replacing the phenyl substituent with 2,4,6-triethylphenyl, the product mixture flipped to favor the 'out' stereoisomer by <1:15 (entry 3), and changing to 2,4,6-trimethoxyphenyl lowered the ratio while still favoring the 'out' isomer by 1:3 (entry 4). Interestingly, when 2,4,6-trimethoxyphenyl substituent was changed to 3,4,5-trimethoxyphenyl, the product mixture again favored the 'in' isomer >15:1 (entry 5). Other less sterically bulky substituents such as cyclohexyl, *trans*-cinnamyl, and *n*-butyl all favored the 'in' stereoisomeric product in a ratio of 12:1 or higher (entries 6–8). *C*-Aliphatic nitrones, ketonitrones and *C*-unsubstituted nitrones are difficult to prepare due to rapid dimerization behavior of aliphatic/unsubstituted nitrones, and facile hydrolysis of ketonitrones. We therefore devised a one-pot method to trap these unstable nitrones by preparing them in situ with ynoate dipolarophiles, which successfully gave the corresponding β-ketoalkylidenes in high yields (entries 8–10).

Alkynes bearing electron-withdrawing groups other than ester were also examined in the [3+2] cyclization/oxidative extrusion reaction sequence (Table 6).

This reaction sequence worked well, giving β-ketoalkylidenes in moderate yield over two steps. Alkynyl ester **9a** was reacted with two different nitrones (entries 1–2), and the relative stereochemistry of the products reflected the substitution pattern of the nitrone utilized: when the nitrone contained a methyl substitution in the alpha position (entry 1), the product favored the 'out' stereoisomer **29b**, however, when the nitrone replaced the methyl group with a hydrogen (entry 2), the product distribution completely reversed to favor the 'in' isomer **30a**. Alkyne **9e** was slow to undergo [3+2] cyclization (entry 6); however, when the temperature was raised above 80 °C, the isoxazoline continued to react to give the β-ketoaziridine, which is a known transformation in the literature.[23] Performing the [3+2] reaction at or below 80 °C circumvented this problem, though cycloaddition of alkynyl sulfone **9e** took 5–8 days to go to completion. Haloalkyne **9f** did not undergo [3+2] reaction and slowly dehalogenated to the terminal alkyne over extended reaction times. In an effort to bolster the reactivity of chloroalkyne **9f**, Lewis acid promoters were added, as these have been used in [3+2] nitrone–alkene cycloadditions to improve regioselectivity.[24] Unfortunately, catalytic and stoichiometric amounts of either $Mg(OTf)_2$ or $Zn(OTf)_2$ were unable to polarize the alkynyl chloride **9f** toward reaction. A survey of the literature revealed surprisingly few examples of [3+2] cyclizations with either alkenyl or alkynyl halides, though the examples found were reported to cyclize in moderate yields.[25]

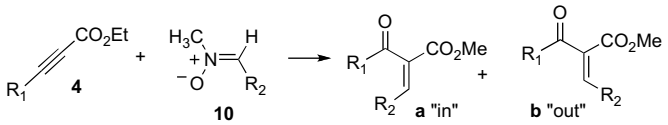
We also attempted the cycloaddition/oxidation sequence to prepare β-diketones (Table 7). Preliminary experiments were run with the *N*-methyl substituted isoxazolines (entries 1 and 2). The results obtained were unexpectedly poor, giving only trace amounts of desired product and a large number of unidentified side products.

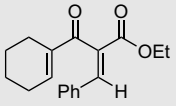
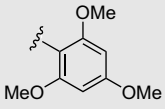
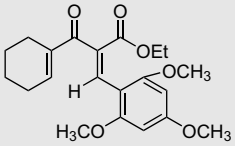
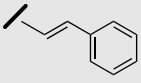
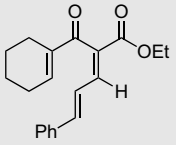
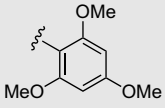
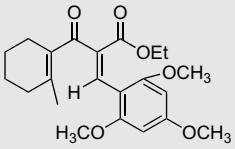
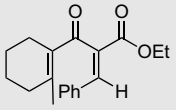
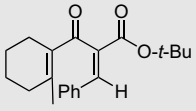
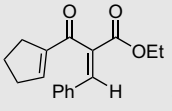
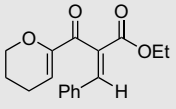
A Hoffman-type[26] elimination of the isoxazolino-*N*-oxide was considered as a decomposition pathway that could be responsible for the poor results (Scheme 3).

It was reasoned that an isoxazoline intermediate without α-hydrogens on the *N*-alkyl substituent would be unable to decompose via Hoffman elimination, so *N*-*tert*-butyl substituted nitrones were tested in the sequence (Table 7, entries 3–5). We were pleased to observe smooth extrusion of the *N*-*tert*-butyl isoxazolines, which gave β-diketones in good yields. Phenyl substitution on the nitrone gave the 'out' isomer in a <1:15 ratio (entry 3), and cyclohexyl completely reversed this selectivity to the 'in' isomer by >15:1 (entry 4). A *trans*-cinnamyl substituent on the nitrone gave a 7:1 ratio favoring the 'in' isomer (entry 5).

In addition to using the [3+2]/[O] sequence to the preparation of β-ketoesters and β-diketones, we attempted to apply these reactions to the synthesis of Baylis–Hillman-type adducts (Scheme 4). The Baylis–Hillman reaction[27] is a popular method of preparing α-alkylidene-β-hydroxyketones, which are valuable building blocks for organic synthesis, especially

Table 4
[3+2]/[O] sequence for the synthesis of divinyl ketones



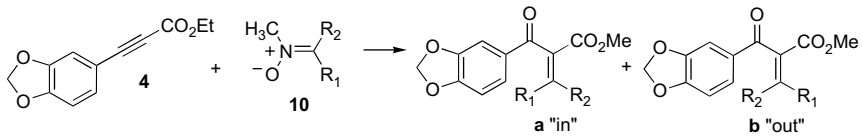
Entry	R^1	R^2	Yield (%) [3+2]	Major product from extrusion	Yield (%) (a+b)	Ratio (a:b)
1		Ph	94	 **11a**	94	>15:1
2			67	 **12a**	96	1:2.6
3			74	 **13a**	83	6:1
4			67	 **14b**	93	1:12
5		Ph	61	 **15a**	85	8:1
6		Ph	[a]	 **16a**	90	6:1
7		Ph	64	 **17a**	64	>15:1
8		Ph	53	 **18a**	35	>15:1

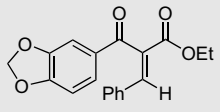
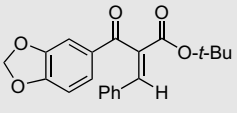
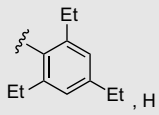
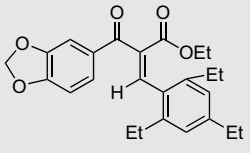
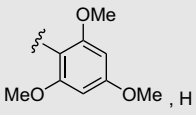
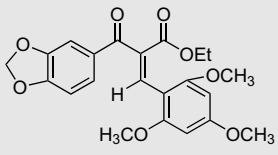
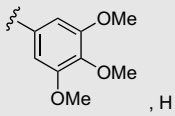
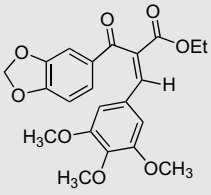
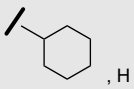
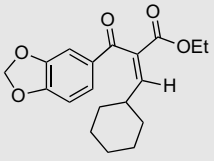
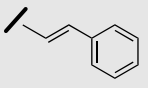
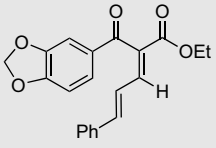
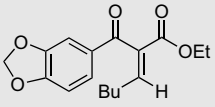
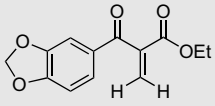
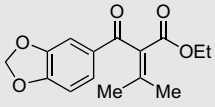
Reaction conditions: i. 1 equiv alkyne, 2 equiv nitrone, 0.2 M toluene, 65 °C, 16 h; ii. 1.5 equiv *m*-CPBA, 0.9 M DCM, 0 °C, 1 h.
[a] Ester=*t*-Bu instead of Et, isoxazoline was not isolated.

in enantiopure form. However, while the Baylis–Hillman reaction is very effective for preparation of α-methylene-β-hydroxyketones (e.g., **43**, R^3=H), reactivity often becomes a problem for more highly substituted analogs. Since an R^3 substituent is easily introduced via a [3+2] cyclization, we sought to provide an alternative method for synthesis of α-alkylidene-β-hydroxyketones of type **43**. It was envisioned that an isoxazoline of type **41** could be reduced to give the corresponding hydroxyisoxazoline **42**, and subsequent oxidation/extrusion would provide the desired Baylis–Hillman adduct **43**. Coupled with an enantioselective reduction of ketone **41**,[28] the strategy could provide chiral products with high enantiomeric excess.

To test this strategy, two complementary isoxazolines **44** and **47** were prepared via [3+2] cyclization. Isoxazoline **44** was reduced under Luche[29] conditions to yield the product alcohol **45** in 70% yield, with a diastereomeric ratio of 1.3:1. Treatment of hydroxyisoxazoline **45** with *m*-CPBA under the standard oxidation conditions led to 73% yield of the desired β-hydroxyketone isomers **46a** and **46b** in a ratio of 1:2 'in':'out' relative to the

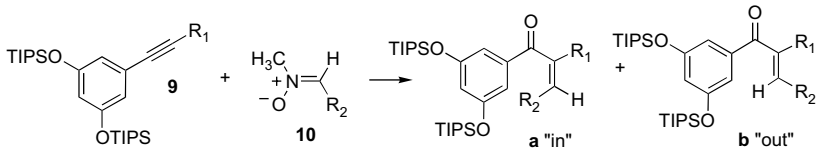
Table 5
Scope of nitrone substitution in the [3+2]/[O] sequence

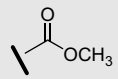
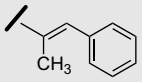
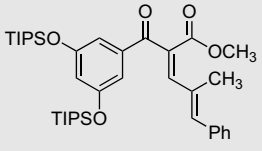
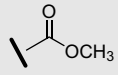
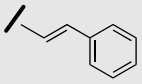
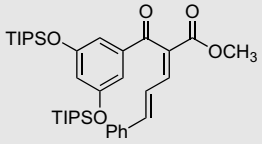
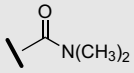
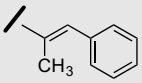
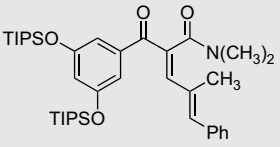
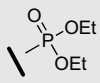
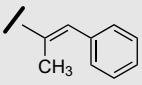
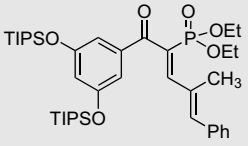
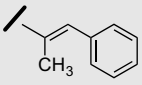
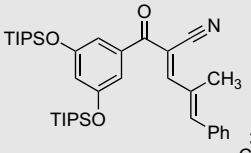
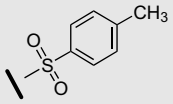
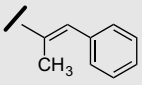
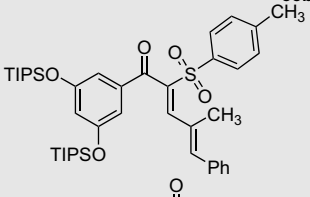
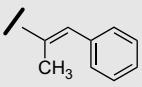
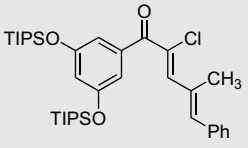


Entry	R^1, R^2	Yield (%) [3+2]	Major product from extrusion	Yield (%) (a+b)	Ratio (a:b)
1	Ph, H	93	 **19a**	85	>15:1
2[a]	Ph, H	[b]	 **20a**	71	8:1
3	 , H	[b]	 **21b**	89	<1:15
4	 , H	[b]	 **22b**	94	1:3
5	 , H	[b]	 **23a**	85	>15:1
6	 , H	86	 **24a**	93	>15:1
7	 , H	95	 **25a**	92	12:1
8	Bu, H[c]	81	 **26a**	95	12:1
9	H, H[c]	85	 **27**	91	n/a
10	Me, Me[c]	79	 **28**	96	n/a

Reaction conditions: i. 1 equiv alkyne, 2 equiv nitrone, 0.2 M toluene, 65 °C, 16 h; ii. 1.5 equiv *m*-CPBA, 0.9 M DCM, 0 °C, 1 h.
[a] Ester=*t*-Bu instead of Et.
[b] Isoxazoline was not isolated, but subjected immediately to the oxidation procedure.
[c] Nitrone prepared in situ from corresponding aldehyde.

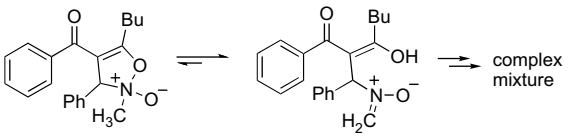
Table 6
[3+2]/[O] sequence applied to alkynes bearing varied electron-withdrawing groups



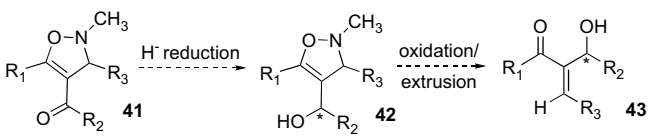
Entry	R^1		R^2	Major product from extrusion	Yield a+b (%)	Ratio (a:b)
1		**9a**		 **29b**	65	<1:19
2[a]		**9a**		 **30a**	67	>19:1
3		**9b**		 **31b**	63	<1:19
4		**9c**		 **32b**	57	<1:19
5		**9d**		 **33b**	57	<1:19
6[b]		**9e**		 **34b**	43	<1:19
7[c]	–Cl	**9f**		 **35b**	—	—

Reaction conditions: i. 1 equiv alkyne, 2 equiv nitrone, 0.2 M toluene, 80 °C, 16 h; ii. 2 equiv *m*-CPBA, 0.2 M CH_2Cl_2, 0 °C, 1 h.
[a] *N*-Methylnitrone prepared from *trans*-cinnamaldehyde was used.
[b] Reaction time=5 days.
[c] Starting material was recovered unreacted, even with 1 equiv $Mg(OTf)_2$ or $Zn(OTf)_2$.

ketone (Eq. 3). Reduction of isomeric isoxazoline **47** with DIBAL[30] successfully gave alcohol **48** in 79% yield as a 3.6:1 mixture of diastereomers. Treatment of hydroxyl isoxazoline **48** with *m*-CPBA gave 73% yield of the desired β-hydroxyketone isomers **49a** and **49b** in a ratio of 1:1 (Eq. 4).[31] So, it was possible to prepare the desired Baylis–Hillman adducts using this method, but mixtures of products were obtained. The reduction of isoxazoline ketones **44** and **47** using simple hydride

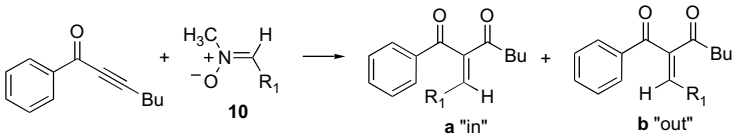


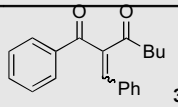
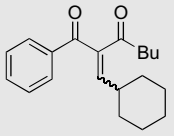
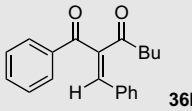
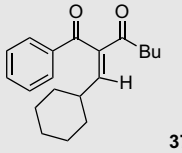
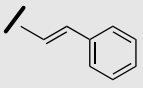
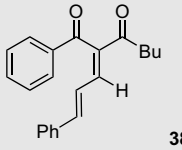
Scheme 3. Potential competing Hoffman elimination pathway.



Scheme 4. Strategy for the preparation of Baylis–Hillman adducts.

Table 7
[3+2]/[O] sequence used to prepare β-diketone systems



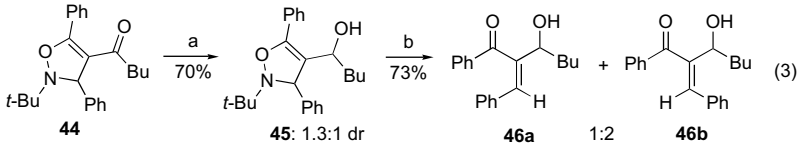
Entry	R^1	R^2	Yield [3+2] (%)	Major product from extrusion	Yield a+b (%)	Ratio (a:b)
1	Me	Ph	92	 **36**	—	—
2	Me		96	 **37**	12	—
3	*t*-Bu	Ph	50	 **36b**	61	<1:15
4	*t*-Bu		83	 **37a**	66	>15:1
5	*t*-Bu		64	 **38a**	63	7:1

Reaction conditions: i. 1 equiv alkyne, 1.5 equiv nitrone, 0.5 M toluene, 65 °C; ii. 1.5 equiv *m*-CPBA, 0.9 M CH_2Cl_2, 0 °C.

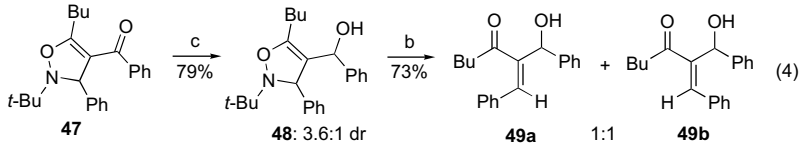
reducing agents was not selective, which complicated analysis of selectivity in the oxidation/extrusion.

Reaction conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; (b) *m*-CPBA, CH_2Cl_2, 0 °C; (c) DIBAL-H, toluene/hexane.

Fortunately, it was possible to separate the two diastereomers of hydroxyisoxazoline **45** by column chromatography and oxidize each diastereomer separately. Oxidation of the minor diastereomer gave a 7.8:1 mixture of products, and oxidation of the major diastereomer gave a 1:1 mixture of products. The complexity of the results obtained with isoxazolines **44** and **47** was discouraging, but our studies have shown that extrusion selectivity is highly substrate-dependent (vide supra), so other isoxazolines may be better candidates for this strategy.



(3)



(4)

3. Discussion

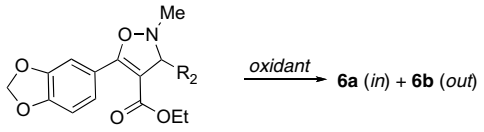
While the sequence represents a useful method for the synthesis of Nazarov cyclization precursors, we did not understand why the reaction was so stereoselective. For the intermediate *N*-oxides **2**, the ring substituent R^2 could rotate either *inward* (to give diastereomer **6a**) or *outward* (to give diastereomer **6b**) during the extrusion (Scheme 5). In the Padwa study, the reaction sequence always gave a single olefin isomer as product.[8] Our experiments confirm the high selectivity of the sequence, and indicate that the olefin geometry of the product can change depending on the substitution pattern of the isoxazoline intermediate. The high torquoselectivities observed in both studies were rather surprising, especially since extrusion was selective for one olefin isomer (**6a**) in some cases and for the isomer with *opposite* olefin geometry (**6b**) in others.

The selectivities observed were not consistent with stereoelectronic predictions,[11a] and there were no obvious nonbonding interactions in the *N*-oxide intermediate that accounted for the product distribution. The 'in'/'out' ratios obtained from extrusion did not match ratios obtained from the analogous Knoevenagel condensation, indicating that the extrusion is not thermodynamically controlled.[32] Another possibility was that selectivity might arise from opposite directions of extrusion for the two diastereomeric *N*-oxide intermediates **2a** and **2b**, i.e., that one isomer undergoes selective *inward* extrusion, and the other selective *outward* extrusion to give the two product isomers **6a** and **6b** (Scheme 5).

Few literature cases of extrusions of this type could be found. One study on a system related to **2** has been reported, describing torquoselective extrusion of dimethylamine from *N*,*N*-dimethyl isoxazolinium salts, via an intermediate without a stereocenter at nitrogen.[33] Like our results, the stereoselectivity in these cases could not be rationalized easily. Since it was not possible to characterize the behavior of the *N*-oxides **2** directly, attempts were made to alter the ratio of *N*-oxides **2** generated in the oxidation step. Different oxidation reagents might have different selectivity for the two faces of the isoxazoline; in which case, we would expect to observe a different ratio of extrusion products **6a** and **6b** with different oxidants. Indeed, extrusion selectivity was slightly different when *m*-CPBA vs oxaziridine **50** was employed in oxidation experiments with two different isoxazolines (Table 8).

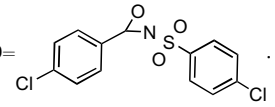
Calculations on the oxidation/extrusion sequence were also performed in collaboration with the Houk group.[34] Oxidation by *m*-CPBA and oxaziridine models was calculated to favor a cis relationship between R_2 and the *N*-methyl group (see **2b**) in order to minimize repulsion between the oxidant and R_2. These results are not consistent with the hypothesis that oxidation stereoselectivity dictates product stereochemistry. The change in the **6a**/**6b** ratio may be explained by the fact that the activation barrier for oxidation by **50** was calculated to be significantly higher (by approximately 14 kcal/mol) than oxidation by *m*-CPBA. A closer interaction between **50** and the isoxazoline exists in this 'later' transition state, which may alter the mode of decomposition of the resulting *N*-oxide. Thus, although experimental data suggests that the *N*-oxide stereochemistry affects torquoselectivity, because a single diastereomer may rotate 'in' or 'out,' depending on the oxidant and the isoxazoline substituents (see Scheme 5), a direct correlation between *N*-oxide stereochemistry and product stereochemistry cannot be made.

Table 8
Extrusion results using different oxidants



R_2	Oxidant[a]	Ratio **6a**/**6b**
2,4,6-Trimethoxyphenyl	*m-CPBA*	1:2
2,4,6-Trimethoxyphenyl	**50**	1:10
Cinnamyl	*m-CPBA*	12:1
Cinnamyl	**50**	7:1

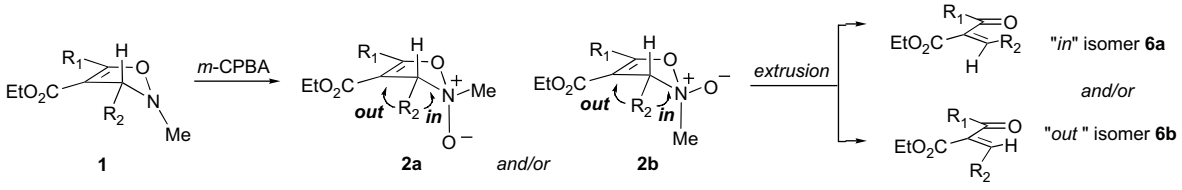
[a] oxidant **50**=



It was found that a diradical species was the most accessible reaction intermediate, consistent with a stepwise rather than a concerted extrusion process. Finally, the calculations predicted torquoselectivity favoring the 'in' products for most substrates, consistent with the experimental findings. The selectivity arose from an extrusion pathway that maintained optimal charge separation in the diradical intermediate. Calculations were also performed on selected cases with 'out' torquoselectivity, which appear to result from subtle nonbonded interactions in the diradical intermediate that can reverse the direction of rotation during extrusion.

4. Summary and conclusions

In summary, a [3+2] cycloaddition/oxidation/extrusion sequence has been developed to synthesize aryl vinyl and divinyl ketones for Nazarov cyclization. The procedure is easy to conduct, and does not require either acidic or basic reaction conditions. Alkynyl esters, sulfones, phosphonates, and amides all participate readily in the reaction. A range of substituents on the electron-deficient alkyne (i.e., R_1) are tolerated, with best results obtained with R_1=aryl. Depending on the substitution pattern, the reaction gave moderate to high selectivities of olefin isomers. The sequence was usually selective for the 'in' extrusion product, although in some cases the 'out' product dominated. It is important to note that both 'in' and 'out' isomers undergo efficient Nazarov cyclization to give the same cyclopentenone product,[32] so this method will be valuable for the synthesis of any Nazarov cyclization substrates, even in the few cases when torquoselectivity is poor. Experimental and computational results show that the extrusion sequence is complicated and that torquoselectivity is not controlled by a single factor. There is strong computational evidence that the sequence proceeds through a stepwise pathway, and that stereoelectronic effects in the diradical intermediate have a strong influence on the



Scheme 5. *N*-Oxide Intermediates in the oxidation/extrusion sequence.

direction of rotation during extrusion.[34] Investigations to further elucidate the mechanism are underway.

5. Experimental section

5.1. General

Reagents were used as obtained from commercial supplier without further purification. Reaction solvents were purchased from Fisher and dispensed using the Glass Contour solvent purification system. ACS grade hexanes and ethyl acetate (EtOAc) are used for column chromatography. Thin layer chromatography (TLC) analysis was determined using precoated silica gel 60 F_{254} glass-supported plate (EMD product). Spots were visualized by UV light (254 nm), or by staining with potassium permanganate or *p*-anisaldehyde solutions followed by heating. Column chromatography separations were carried out on silica gel 60 (230–400 mesh) (EMD product).

^{1}H NMR spectra were recorded on either a 400 MHz or a 500 MHz Avance spectrometer. ^{13}C NMR spectra were recorded on either a 100 MHz or 125 MHz Avance spectrometer. Product *E*/*Z* stereochemistry was assigned based on carbon–hydrogen coupling constants obtained for the ester and(or) the ketone of the divinyl ketone, according to Kingsbury et al.[22] Infrared spectra were recorded on a 8400s Shimadzu FTIR spectrometer using NaCl plates. High resolution mass spectra were done on a ThermoFinnigan MAT 95XL (ESI) at the Chemistry Instrumentation Center of the University of Buffalo.

5.2. Preparation of electron-deficient alkynes

Alkynyl esters **4a**–**4d** were prepared from commercially available aldehydes using the Corey–Fuchs protocol,[14] followed by carboalkoxylation of the resulting terminal alkyne with the appropriate chloroformate. A full description of the preparation of alkynes **9a**–**9f** can be found in the supplementary data accompanying Ref. 32.

*5.2.1. 2-(Benzo[1,3]dioxole)-propynoic acid ethyl ester (**4a**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, J=8.0 Hz, 1H), 6.95 (s, 1H), 6.75 (d, J=8.0 Hz, 1H), 5.97 (s, 2H), 1.5 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 149.7, 147.5, 128.5, 112.8, 112.3, 108.6, 101.6, 84.1, 83.2, 80.9, 65.8, 28.0, 27.3, 15.2. IR (neat) cm^{-1}: 2213, 1706, 1105. HRMS (*m*/*z*): calcd for $C_{14}H_{14}O_4Na$ [M−Na$^+$], 269.0771; found, 269.0777.

*5.2.2. (5,6-Dihydro-4H-pyran-2-yl)-propynoic acid ethyl ester (**4b**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.48 (m, 1H), 4.18 (q, J=7.0 Hz, 2H), 3.99 (m, 2H), 2.09 (m, 2H), 1.80 (m, 2H), 1.24 (t, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 135.6, 114.9, 81.3, 78.5, 66.4, 61.8, 21.2, 20.9, 13.8. IR (neat) cm^{-1}: 2976, 2936, 1712, 1463, 1444, 1244. HRMS (*m*/*z*): calcd for $C_{10}H_{12}O_3$ [M$^+$], 180.0781; found, 180.0786.

*5.2.3. (2-Methyl-cyclohex-1-enyl)-propynoic acid ethyl ester (**4c**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (q, 2H J=7.2 Hz), 2.05 (s, 2H), 1.98 (s, 2H), 1.82 (s, 3H), 1.5 (m, 4H), 1.19 (t, 3H J=7.2 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 154.1, 149.5, 111.9, 87.0, 82.9, 61.2, 31.3, 28.5, 22.4, 22.1, 21.8, 13.7. IR (neat) cm^{-1}: 2981, 2933, 2862, 2825, 2208, 2192, 1745, 1704, 1629, 1442, 1423, 1365, 1336, 1282, 1259, 1215, 1178, 1143, 1095, 1024, 748. HRMS (*m*/*z*): calcd for $C_{12}H_{17}O_2$ [M−H$^+$], 193.1223; found, 193.1215.

*5.2.4. (1-Hydroxy-cyclopentyl)-propynoic acid ethyl ester (**4d**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.33 (m, 1H), 4.12 (q, J=7.0 Hz, 2H), 2.45 (m, 4H), 1.88 (m, 2H), 1.24 (t, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 149.6, 121.8, 83.5, 81.7, 61.6, 35.4, 33.5, 23.0, 13.8. IR (neat) cm^{-1}: 2935, 2202, 1704, 1446, 1365, 1265, 1207, 1141. HRMS (*m*/*z*): calcd for $C_{10}H_{13}O_2$ [M−H$^+$], 165.0910; found, 165.19189.

5.3. Preparation of nitrones

Nitrones **10a**–**10d** and **10h**–**j** are known compounds and were prepared using the general procedure described below. Typically, the nitrones were not purified, but isolated in crude form and used directly in the [3+2] dipolar cycloaddition.

5.3.1. Representative procedure for preparation of nitrones

In a 250 mL round-bottom flask, $MgSO_4$ (10.5 g), $NaHCO_3$ (14.7 g, 0.2 mol), and *N*-methylhydroxylamine·HCl (7.6 g, 0.1 mol) were combined, and CH_2Cl_2 (75 mL) was added with the appropriate aldehyde (36.0 mmol). The solution was stirred for 6 h, then concentrated. The crude mixture was purified by column chromatography (2:1 hexanes/ethyl acetate) to give the nitrone.

*5.3.2. Methanamine, N-((2,4,6-trimethoxyphenyl)methylene)-N-oxide (**10e**)*

Prepared as above. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (s, 1H), 6.13 (s, 2H), 2.88 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 159.8, 130.2, 101.4, 90.7, 55.8, 55.4, 53.4. IR (neat) cm^{-1}: 3048, 3014, 2934, 2838, 1606, 1575, 1499, 1456, 1407, 1398. HRMS: calcd for $C_{12}H_{15}ON_2Na$ [M−Na$^+$], 226.1077; found, 226.1077.

*5.3.3. Methanamine, N-((3,4,5-trimethoxyphenyl)methylene)-N-oxide (**10f**)*

Prepared as above. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (s, 2H), 3.81 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 139.7, 134.8, 125.9, 105.7, 60.7, 56.0, 54.1. IR (neat) cm^{-1}: 3116, 3015, 2964, 2935, 2831, 1583, 1568, 1497, 1471, 1454, 1435, 1412, 1400, 1338, 1306, 1232, 1167. HRMS: calcd for $C_{11}H_{16}O_4N$ [M−H$^+$], 226.1074; found, 226.1072.

*5.3.4. Methanamine, N-((2,4,6-trimethylphenyl)methylene)-N-oxide (**10g**)*

Prepared as above. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 6.93 (s, 2H), 3.83 (s, 3H), 2.5 (m, 6H), 1.19 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 143.4, 135.4, 125.4, 124.8, 87.4, 53.0, 44.1, 28.8, 26.7, 15.4, 15.1. HRMS: calcd for $C_{14}H_{22}ON$ [M−H$^+$], 220.1694; found, 220.1678.

5.4. General procedures for the [3+2] cycloaddition/cheletropic extrusion sequence

5.4.1. General procedure A for the preparation of isoxazolines ([3+2] cycloaddition)

Alkyne (0.56 mmol) and nitrone (1.23 mmol) were covered with toluene (0.5 mL) at rt under argon. The resulting suspension was heated to 65 °C and stirred until completion as indicated by TLC (about 18 h). The reaction mixture was loaded directly onto a silica gel column and eluted with ethyl acetate/hexane to give the isoxazoline product.

5.4.2. General procedure B for the preparation of isoxazolines ([3+2] cycloaddition)

Alkyne (0.48 mmol), aldehyde (0.72 mmol), *N*-methylhydroxylamine hydrochloride (0.64 mmol), and diisopropylethyl amine (0.64 mmol) were all combined at rt, covered with ethanol (0.30 mL) and heated to 50 °C for 12 h. The resulting solution was then heated to 80 °C for another 12 h. The solution was cooled to rt, diluted with Et_2O (2 mL), washed with satd NH_4Cl (2×1 mL), brine (1 mL), dried over $MgSO_4$ and concentrated. Purification by column chromatography (ethyl acetate/hexane) gave the desired isoxazoline.

5.4.3. General procedure C (oxidation of isoxazoline intermediate)

m-CPBA (0.20 mmol) was added to a solution of isoxazoline (0.14 mmol) in DCM (0.16 mL) at 0 °C. The reaction was stirred at 0 °C until complete by TLC (about 5 min). The reaction was diluted with Et_2O (1 mL), washed with 1 M NaOH (1 mL), and the organic layer was dried over $MgSO_4$ and concentrated. Column chromatography (ethyl acetate/hexane) gave the desired product.

5.4.4. General procedure D (one-pot [3+2] cycloaddition/oxidation)

In a dry 100 mL round-bottom flask was weighed the nitrone (8.0 mmol), alkyne (7.1 mmol), and toluene (35 mL), and the solution was heated at 80 °C for 16 h. The solution was concentrated, and CH_2Cl_2 (35 mL) was added, cooled to −20 °C, and *m*-CPBA (11.6 mmol) was added and stirred for 30 min. The reaction was quenched with saturated Na_2SO_3 (50 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×50 mL), the organic phases were combined and washed with brine (50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography (ethyl acetate/hexane).

5.5. Preparation of aryl vinyl and divinyl ketones

*5.5.1. 2-(Cyclohex-1-enecarbonyl)-3-phenyl-acrylic acid ethyl ester (**11a**)*

The intermediate isoxazoline (*5-cyclohex-1-enyl-2-methyl-3-phenyl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (88% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.37 (m, 5H), 6.5 (m, 1H), 4.93 (s, 1H), 2.92 (s, 3H), 2.22–2.5 (m, 4H), 1.66–1.73 (m, 4H), 1.14 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 141.6, 135.8, 128.2, 127.5, 127.0, 126.2, 109.3, 102.3, 76.3, 59.5, 46.8, 31.4, 26.0, 25.5, 22.1, 21.4, 13.9. IR (neat) cm^{-1}: 2817, 2269, 1703, 1618, 1501, 1475, 1392, 1315, 1225, 1068, 911. HRMS (*m*/*z*): calcd for $C_{19}H_{23}NO_3$ [M$^+$], 313.1672; found, 313.1668.

General procedure C provided the title compound (**11a**) from the intermediate isoxazoline (94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.32 (m, 5H), 6.82 (m, 1H), 4.27 (q, J=7.2 Hz, 2H), 2.35 (m, 2H), 2.13 (m, 2H), 1.68–1.55 (m, 4H), 1.28 (t, J=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.5, 165.1, 144.6, 141.3, 139.2, 133.2, 131.7, 129.9, 129.8, 128.5, 61.2, 26.1, 22.6, 21.6, 21.3, 14.0. IR (neat) cm^{-1}: 3050, 3020, 2974, 2924, 2860, 1662, 1654, 1633, 1570, 1497, 1448, 1250, 1190. HRMS (*m*/*z*): calcd for $C_{18}H_{20}O_3$ [M$^+$], 284.1407; found, 284.1411. J_{C-H}: 7.8 Hz.

*5.5.2. 2-(Cyclohex-1-enecarbonyl)-3-(2,4,6-trimethoxy-phenyl)-acrylic acid ethyl ester (**12b**)*

The intermediate isoxazoline (*2-methyl-5-(2-methyl-cyclohex-1-enyl)-3-(2,4,6-trimethoxy-phenyl)-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (67% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.31 (s, 1H), 6.08 (s, 2H), 5.65 (s, 1H), 3.93 (m, 2H), 3.76 (m, 9H), 2.87 (s, 3H), 2.36–2.17 (m, 4H), 1.67 (m, 4H), 1.03 (t, J=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.44, 164.42, 160.5, 159.6, 133.6, 127.0, 110.5, 99.8, 90.8, 67.1, 58.9, 55.7, 55.0, 47.9, 26.1, 25.3, 22.2, 21.5, 13.8. IR (neat) cm^{-1}: 2996, 2971, 2942, 2928, 2852, 2840, 1672, 1649, 1625, 1606, 1588. HRMS (*m*/*z*): calcd for $C_{22}H_{30}NO_6$ [M−H$^+$], 404.2068; found, 404.2074.

General procedure C provided the title compound (**12b**) from the intermediate isoxazoline (96% combined yield with **12a**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.53 (dd, J_{ab}=8.0 Hz, J_{ac}=1.5 Hz, 1H), 6.80 (d, J=8.0 Hz, 1H), 6.59 (s, 2H), 6.03 (s, 2H), 4.25 (q, J=7.0 Hz, 2H), 3.79 (s, 3H), 3.66 (s, 6H), 1.21 (t, J=7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 167.0, 163.2, 159.4, 141.1, 138.5, 134.8, 129.3, 105.5, 90.2, 90.1, 65.8, 35.4, 35.3, 35.0, 26.0, 23.0, 22.1, 21.8, 14.2. IR (neat) cm^{-1}: 2928, 2850, 2841, 2832, 1706, 1646, 1629, 1607, 1584, 1508. HRMS (*m*/*z*): $C_{21}H_{27}O_6$ [M−H$^+$], 375.1738; found, 375.1711. J_{C-H}: 9.3 Hz.

*5.5.3. 2-(Cyclohex-1-enecarbonyl)-5-phenyl-penta-2,4-dienoic acid ethyl ester ((E)-**13a**)*

The intermediate isoxazoline (*5-cyclohex-1-enyl-2-methyl-3-styryl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 6.66 (d, J=16 Hz, 1H), 6.48 (m, 1H), 6.28 (dd, J_{ab}=16 Hz, J_{ac}=7 Hz, 1H), 4.60 (d, J=7 Hz, 1H), 4.19–4.11 (m, 2H), 2.85 (s, 3H), 2.42 (m, 1H), 2.21 (m, 3H), 1.72–1.65 (m, 4H), 1.26 (t, J=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 136.8, 135.9, 130.6, 128.3, 127.6, 127.4, 126.4, 126.3, 100.6, 74.0, 59.6, 45.9, 26.0, 25.5, 22.1, 21.4, 14.1. IR (neat) cm^{-1}: 2913, 2842, 1784, 1614. HRMS (*m*/*z*): calcd for $C_{21}H_{25}NO_3Na$ [M−Na$^+$], 362.1727; found, 362.1722.

General procedure C provided (***E***)-**13a** as a 6:1 ratio of isomers with (***Z***)-**13b**. The isomers could be separated by column chromatography on silica, eluting with ethyl acetate/hexanes: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53–7.31 (m, 6H), 6.99 (d, J=15.0 Hz, 1H), 6.77–6.69 (m, 2H), 4.24 (q, J=7.0 Hz, 2H), 2.39 (m, 2H), 2.24 (m, 2H), 1.73–1.63 (m, 4H), 1.27 (q, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0, 165.1, 144.8, 142.5, 142.0, 140.2, 135.6, 132.0, 129.3, 128.6, 127.6, 127.4, 123.2, 109.5, 60.8, 26.2, 22.6, 21.7, 21.4, 14.0. IR (neat) cm^{-1}: 3050, 3020, 2974, 2924, 2860, 2842, 2753, 1684, 1674, 1603, 1542, 1505, 1448, 1250, 1190. HRMS: calcd for $C_{21}H_{25}O_3$ [M−H$^+$], 325.1785; found, 325.1787. **(*Z*)-13b** δ 7.82 (m, 1H), 1.53 (m, 2H), 7.35 (m, 4H), 6.98–6.94 (m, 2H), 6.69 (m, 1H), 4.28 (q, J=7.0 Hz, 2H), 2.33 (m, 2H), 2.24 (m, 2H), 1.67 (m, 4H), 1.30 (t, J=7.0 Hz, 3H). J_{C-H}: 7.8 Hz.

*5.5.4. 2-(2-Methyl-cyclohex-1-enecarbonyl)-3-(2,4,6-trimethoxy-phenyl)-acrylic acid ethyl ester (**14b**)*

The intermediate isoxazoline (*2-methyl-5-(2-methyl-cyclohex-1-enyl)-3-(2,4,6-trimethoxy-phenyl)-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (49% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 2H), 5.70 (s, 1H), 3.78–4.00 (m, 2H), 3.78 (s, 9H), 2.94 (s, 3H), 2.30–2.68 (m, 2H), 2.05 (m, 2H), 1.73 (s, 3H), 1.66 (m, 4H), 1.06 (t, J=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 164.1, 160.5, 159.6, 137.2, 120.3, 109.3, 90.9, 66.9, 58.8, 55.6, 55.1, 31.2, 27.8, 22.4, 22.3, 20.5, 14.0. IR (neat) cm^{-1}: 2998, 2971, 2940, 2926, 2852, 2840, 1672, 1606, 1588. HRMS (*m*/*z*): calcd for $C_{23}H_{32}NO_6$ [M−H$^+$], 418.2224; found, 418.2236.

General procedure C provided the title compound (**14b**) from the intermediate isoxazoline (96% combined yield with **14a**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 1H), 6.07 (s, 2H), 4.18 (q, J=7.5 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 6H), 2.24 (m, 2H), 2.03 (m, 2H), 1.70 (s, 3H), 1.65 (m, 4H), 1.23 (t, J=7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 167.4, 163.6, 159.9, 136.9, 134.7, 133.4, 132.9, 105.7, 90.3, 60.3, 55.45, 55.43, 31.3, 27.4, 22.6, 22.3, 21.1, 14.1. IR (neat) cm^{-1}: 2926, 2852, 2841, 2830, 1707, 1646, 1629, 1607, 1584, 1508. HRMS (*m*/*z*): calcd for $C_{22}H_{29}O_6$ [M−H$^+$], 389.1935; found, 389.1944. J_{C-H}: 12.4 Hz.

*5.5.5. 2-(2-Methyl-cyclohex-1-enecarbonyl)-3-phenyl-acrylic acid ethyl ester (**15a**)*

The intermediate isoxazoline (*2-methyl-5-(2-methyl-cyclohex-1-enyl)-3-phenyl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (61% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J=7.2 Hz, 2H), 7.33 (t, J=6.8 Hz, 1H), 7.27 (m, 1H), 4.09–3.98 (m, 2H), 2.96 (s, 3H), 2.23 (m, 2H), 2.06 (m, 2H), 1.72 (s, 3H), 1.68 (m, 4H), 1.14 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 163.7, 142.2, 138.1, 182.2, 127.5, 127.0, 119.6, 103.9, 75.8, 59.4, 47.2, 31.2, 27.7, 22.3, 22.2, 20.6, 13.9. IR (neat) cm^{-1}: 2977, 2927, 2858, 2360, 2337, 1693, 1627, 1442, 1373, 1330,

1276, 1234, 1172, 1076. HRMS (*m*/*z*): calcd for $C_{20}H_{26}NO_3$ [M−H$^+$], 328.1907; found, 328.1915.

General procedure C provided the title compound (**15a**) from the intermediate isoxazoline (85% combined yield with **15b**) and characterized as a 2:1 mixture. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.47 (m, 2.5H), 7.33 (m, 5H), 4.35 (m, 2.82H), 2.23 (m, 0.9H), 2.18 (m, 2H), 2.10 (m, 3H), 2.02 (s, 3H), 1.70 (m, 2.5H), 1.48 (m, 4.5H), 1.26 (m, 4.6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 194.6, 165.3, 149.5, 142.7, 140.4, 135.6, 134.7, 133.5, 133.2, 131.87, 131.83, 131.5, 130.6, 129.9, 129.7, 129.6, 128.8, 128.5, 61.5, 61.3, 34.5, 31.1, 27.3, 26.3, 22.48, 22.46, 22.3, 22.1, 22.0, 21.1, 14.2, 13.9. IR (neat): 3051, 3022, 2974, 2924, 2862, 1662, 1654, 1636, 1570, 1497, 1448, 1253, 1192. HRMS (*m*/*z*): calcd for $C_{19}H_{22}O_3$ [M$^+$], 298.1563; found, 298.1567.

5.5.6. 2-(Cyclopent-1-enecarbonyl)-3-phenyl-acrylic acid ethyl ester (*17a*)

The intermediate isoxazoline (*2-methyl-5-(2-methyl-cyclohex-1-enyl)-3-phenyl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (89% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.38 (m, 5H), 6.92 (m, 1H), 4.98 (s, 1H), 4.04 (m, 2H), 2.92 (s, 3H), 2.52–2.81 (m, 4H), 1.98 (m, 2H), 1.13 (t, *J*=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 158.7, 141.7, 141.5, 130.8, 128.2, 127.5, 127.1, 103.3, 59.6, 46.8, 33.5, 23.1, 13.9. IR (neat) cm^{-1}: 3093, 3035, 2958, 2939, 2906, 2873, 2852, 1703, 1681, 1610, 1581, 1456, 1392, 1371, 1323, 1298, 1276, 1261, 1232, 1195, 1172, 1130, 1074, 950. HRMS (*m*/*z*): calcd for $C_{18}H_{21}NO_3$ [M$^+$], 299.1516; found, 299.1510.

General procedure C provided the title compound (**17a**) from the intermediate isoxazoline (64% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.35 (m, 5H), 6.60 (s, 1H), 4.26 (q, *J*=7.2 Hz, 2H), 2.65 (m, 2H), 2.43 (m, 2H), 1.99 (m, 2H), 1.33 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 165.1, 148.3, 145.4, 141.2, 133.2, 132.3, 130.1, 129.9, 128.7, 61.4, 34.0, 30.2, 22.9, 14.1. IR (neat) cm^{-1}: 2974, 2955, 1714, 1703, 1650, 1609, 1448. HRMS (*m*/*z*): calcd for $C_{17}H_{18}O_3$ [M$^+$], 269.1172; found, 269.1175. J_{C-H}: 7.8 Hz.

5.5.7. 2-(5,6-Dihydro-4H-pyran-2-carbonyl)-3-phenyl-acrylic acid ethyl ester ((*E*)-*18a*)

The intermediate isoxazoline (*5-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (53% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H), 5.71 (t, *J*=4 Hz, 1H), 4.97 (s, 1H), 4.14–4.03 (m, 4H), 2.93 (s, 3H), 2.22 (m, 2H), 1.92 (m, 2H), 1.14 (t, *J*=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 156.5, 142.2, 140.8, 128.2, 127.7, 127.2, 109.0, 104.5, 76.6, 66.4, 59.8, 46.6, 21.7, 20.4, 13.9. IR (neat) cm^{-1}: 3028, 2927, 2874, 2840, 1700, 1685, 1666, 1607, 1453, 1391, 1387, 1371. HRMS: calcd for $C_{18}H_{21}O_4N$ [M$^+$], 315.1465; found, 315.1466.

General procedure C provided the title compound (**18a**) from the intermediate isoxazoline. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.39–7.33 (m, 5H), 6.00 (t, *J*=4.5 Hz, 1H), 4.28 (t, *J*=7.0 Hz, 2H), 4.07 (m, 2H), 2.14 (m, 2H), 1.82 (m, 2H), 1.29 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 164.9, 151.2, 142.9, 133.0, 130.3, 130.2, 128.7, 116.0, 66.5, 61.5, 21.3, 21.0, 14.1. IR (neat) cm^{-1}: 3070, 3000, 2945, 2892, 2860, 1675, 1614, 1601, 1570, 1497, 1448, 1250, 1190. J_{C-H}: 7.3 Hz.

5.5.8. 2-(Benzo[1,3]dioxole-5-carbonyl)-3-phenyl-acrylic acid ethyl ester (*19a*)

The intermediate isoxazoline (*5-benzo[1,3]dioxol-5-yl-2-methyl-3-phenyl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, *J*=8 Hz, 1H), 7.43 (m, 3H), 7.37 (t, *J*=7 Hz, 2H), 7.31 (m, 1H), 6.84 (d, *J*=8 Hz, 1H), 6.05 (s, 2H), 5.07 (s, 1H), 4.11 (q, *J*=7 Hz, 2H), 3.01 (s, 3H), 1.14 (t, *J*=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 161.1, 150.0, 147.2, 141.6, 128.4, 127.8, 127.2, 125.1, 120.7, 110.2, 107.8, 102.6, 101.5, 76.8, 60.0, 53.4, 14.0. IR (neat) cm^{-1}: 3101, 3015, 2981, 2897, 1701, 1692, 1633, 1604, 1488, 1446, 1326, 1255, 1232, 1074, 1039, 813. HRMS (*m*/*z*): calcd for $C_{20}H_{20}NO_5$ [M−H$^+$], 354.1336; found, 354.1341.

General procedure C provided the title compound (**19a**) from the intermediate isoxazoline (94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.51 (d, *J*=8.0 Hz, 1H), 7.48 (s, 1H), 7.37–7.22 (m, 5H), 6.78 (d, *J*=8.0 Hz, 1H), 6.02 (s, 1H), 4.25 (q, *J*=7.2 Hz, 2H), 1.21 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 165.0, 152.6, 148.4, 142.1, 132.8, 131.3, 130.3, 130.1, 128.7, 126.4, 108.1, 102.0, 61.5, 14.1. IR (neat) cm^{-1}: 2980, 2903, 1712, 1658, 1600, 1502, 1486, 1438, 1244. HRMS (*m*/*z*): calcd for $C_{19}H_{16}O_5$ [M−H$^+$], 325.1071; found, 325.1076. J_{C-H}: 7.8 Hz.

5.5.9. 2-(Benzo[1,3]dioxole-5-carbonyl)-3-(2,4,6-triethyl-phenyl)-acrylic acid ethyl ester (*21b*)

The intermediate isoxazoline (*5-benzo[1,3]dioxol-5-yl-2-methyl-3-(2,4,6-triethyl-phenyl)-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (38% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J*=8.5 Hz, 1H), 7.33 (s, 1H), 6.88 (m, 2H), 6.02 (s, 2H), 5.75 (s, 1H), 3.95 (m, 2H), 3.05 (s, 3H), 2.98–2.84 (m, 4H), 2.60 (q, *J*=7.5 Hz, 2H), 1.23 (m, 9H), 0.95 (t, *J*=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 160.7, 149.6, 147.1, 143.5, 131.7, 126.7, 124.3, 121.1, 109.8, 107.8, 103.2, 101.4, 73.4, 59.6, 47.8, 28.4, 16.3, 15.3, 13.7. IR (neat) cm^{-1}: HRMS (*m*/*z*): calcd for $C_{26}H_{32}NO_5$ [M−H$^+$], 438.2275; found, 438.2268.

General procedure C provided the title compound (**21b**) from the intermediate isoxazoline (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.5 (d, *J*=8.0 Hz, 1H), 7.41 (s, 1H), 6.9 (s, 2H), 6.88 (d, *J*=8.0 Hz, 1H), 6.06 (s, 2H), 3.98 (q, *J*=7.0 Hz, 2H), 2.60 (m, 6H), 1.26–1.17 (m, 9H), 0.89 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 164.9, 151.9, 148.2, 144.8, 140.7, 137.5, 131.6, 130.2, 125.6, 125.0, 108.8, 107.8, 101.9, 60.8, 28.6, 26.9, 15.5, 14.8, 13.4. IR (neat) cm^{-1}: 2963, 2930, 2871, 1728, 1603, 1483, 1439, 1371. HRMS (*m*/*z*): calcd for $C_{25}H_{29}O_5$ [M−H$^+$], 409.2010; found, 409.2013. J_{C-H}: 12.4 Hz.

5.5.10. 2-(Benzo[1,3]dioxole-5-carbonyl)-3-(2,4,6-trimethoxy-phenyl)-acrylic acid ethyl ester (*22b*)

The intermediate isoxazoline (*5-benzo[1,3]dioxol-5-yl-2-methyl-3-(2,4,6-trimethoxy-phenyl)-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J*=8.4 Hz, 1H), 7.39 (s, 1H), 6.83 (d, *J*=8 Hz, 1H), 6.10 (s, 2H), 5.97 (s, 2H), 5.75 (s, 1H), 3.96 (m, 2H), 3.76 (m, 9H), 2.96 (s, 3H), 1.02 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 161.2, 160.7, 159.6, 149.3, 146.9, 124.2, 121.6, 109.8, 107.6, 101.2, 100.2, 90.9, 67.6, 60.2, 59.1, 55.8, 55.1, 13.8. IR (neat) cm^{-1}: 2999, 2976, 2949, 2932, 2874, 1690, 1636, 1591, 1505, 1487. HRMS (*m*/*z*): calcd for $C_{23}H_{26}NO_8$ [M−H$^+$], 444.1653; found, 444.1655.

General procedure C provided the title compound (**22b**) from the intermediate isoxazoline (94% combined yield with **22a**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.47 (d, *J*=8.0 Hz, 1H), 7.42 (s, 1H), 6.78 (d, *J*=8.0 Hz, 1H), 6.01 (s, 2H), 5.96 (s, 2H), 4.19 (q, *J*=7.2 Hz, 2H), 3.77 (s, 3H), 3.51 (s, 6H), 1.56 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.0, 176.6, 166.7, 163.4, 159.6, 150.9, 147.7, 135.5, 132.8, 128.7, 125.1, 108.3, 107.5, 105.1, 101.6, 90.2, 60.8, 55.3, 54.7, 14.1. IR (neat) cm^{-1}: 2975, 2938, 2901, 2839, 1703, 1661, 1598, 1573, 1436. HRMS (*m*/*z*): calcd for $C_{22}H_{22}O_8Na$ [M−Na$^+$], 415.1387; found, 415.1393. J_{C-H}: 8.5 Hz.

5.5.11. 2-(Benzo[1,3]dioxole-5-carbonyl)-3-(3,4,5-trimethoxy-phenyl)-acrylic acid ethyl ester (*23a*)

The intermediate isoxazoline (*5-benzo[1,3]dioxol-5-yl-2-methyl-3-(3,4,5-trimethoxy-phenyl)-2,3-dihydro-isoxazole-4-carboxylic acid*

ethyl ester) was prepared according to general procedure A (70% yield). ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.46 (d, J=8 Hz, 1H), 7.44 (s, 1H), 6.83 (d, J=8 Hz, 1H), 6.64 (s, 2H), 5.98 (s, 2H), 4.99 (s, 1H), 4.09 (q, J=7.2 Hz, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 2.98 (s, 3H), 1.14 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 161.0, 153.2, 150.0, 147.2, 137.5, 137.1, 125.0, 120.6, 110.1, 107.8, 104.0, 102.4, 101.5, 60.6, 59.9, 56.0, 46.8, 20.9, 14.1. IR (neat) cm^{-1}: 2968, 2942, 2926, 2901, 2829, 1765, 1688, 1635, 1592, 1504, 1486, 1442, 1421. HRMS (m/z): calcd for $C_{23}H_{26}NO_8$ [M−H$^+$], 444.1653; found, 444.1654.

General procedure C provided the title compound (**23a**) from the intermediate isoxazoline (85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.45 (s, 1H), 6.80 (d, J=8.0 Hz, 1H), 6.59 (s, 2H), 6.04 (s, 2H), 4.24 (q, J=7.2 Hz 2H), 3.80 (s, 3H), 3.68 (s, 6H), 1.22 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 165.0, 152.9, 152.6, 148.4, 142.0, 139.9, 131.2, 130.3, 128.1, 126.2, 108.2, 108.0, 107.6, 102.0, 61.4, 60.8, 55.8, 14.0. IR (neat) cm^{-1}: 2937, 2903, 2838, 1712, 1657, 1601, 1579, 1503, 1486, 1439, 1244. HRMS (m/z): calcd for $C_{22}H_{23}O_8$ [M−H$^+$], 415.1387; found, 415.1387. J_{C-H}: 8.3 Hz.

5.5.12. 2-(Benzo[1,3]dioxole-5-carbonyl)-3-cyclohexyl-acrylic acid ethyl ester (**24a**)

The intermediate isoxazoline (*5-benzo[1,3]dioxol-5-yl-3-cyclohexyl-2-methyl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J=8 Hz, 1H), 7.33 (s, 1H), 6.83 (d, J=8 Hz, 1H), 6.00 (s, 2H), 4.17 (q, J=7 Hz, 2H), 3.87 (d, J=6.6 Hz, 1H), 2.81 (s, 3H), 1.17–1.34 (m, 13H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6, 161.2, 125.0, 121.2, 110.2, 107.7, 101.4, 77.8, 59.8, 47.6, 42.0, 29.7, 26.7, 26.5, 26.4, 26.2, 14.2. IR (neat) cm^{-1}: 2970, 2956, 2849, 1769, 1693, 1606, 1589, 1503, 1490, 1448, 1357, 1344, 1241, 1067, 1082, 947. HRMS (m/z): calcd for $C_{20}H_{26}NO_5$ [M−H$^+$], 360.1805; found, 360.1811.

General procedure C provided the title compound (**24a**) from the intermediate isoxazoline (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 2H), 6.94 (d, J=10.8 Hz, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.06 (s, 2H), 4.16 (q, J=7.2 Hz, 2H), 2.17 (m, 1H), 1.64 (m, 5H), 1.14 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 164.8, 152.3, 152.1, 148.2, 131.9, 131.7, 126.2, 108.1, 107.9, 101.9, 61.0, 38.5, 31.5, 25.4, 24.9, 13.9. IR (neat) cm^{-1}: 2924, 2850, 1715, 1663, 1602, 1503, 1486, 1439. HRMS (m/z): calcd for $C_{19}H_{22}O_5Na$ [M−Na$^+$], 353.1359; found, 353.1359. J_{C-H}: 8.6 Hz.

5.5.13. 2-(Benzo[1,3]dioxole-5-carbonyl)-5-phenyl-penta-2,4-dienoic acid ethyl ester (**25a**)

The intermediate isoxazoline (*5-benzo[1,3]dioxol-5-yl-2-methyl-3-styryl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure A (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J=8 Hz, 1H), 7.42 (m, 3H), 7.30 (m, 2H), 7.23 (m, 1H), 6.86 (d, J=8.5 Hz, 1H), 6.72 (d, J=16 Hz, 1H), 6.36 (dd, J_{ab}=16 Hz, J_{ac}=6.5 Hz, 1H), 5.99 (s, 2H), 4.75 (d, J=6.5 Hz, 1H), 4.20 (m, 2H), 2.95 (s, 3H), 1.27 (t, J=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 161.2, 150.0, 147.2, 136.8, 131.0, 128.5, 127.6, 127.4, 126.6, 125.0, 120.8, 110.1, 107.8, 101.5, 101.0, 74.5, 60.1, 46.1, 14.2. IR (neat) cm^{-1}: 3031, 2981, 2964, 2904, 1764, 1701, 1632, 1613, 1600, 1503. HRMS (m/z): calcd for $C_{22}H_{22}NO_5$ [M−H$^+$], 308.1492; found, 380.1499.

General procedure C provided the title compound (**25a**) from the intermediate isoxazoline (92% combined yield with **25b**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J=11.6 Hz, 1H), 7.49–7.30 (m, 7H), 7.05 (d, J=15.4 Hz, 1H), 6.86 (d, J=8.5 Hz, 1H), 6.78 (dd, J_{ab}=15.4 Hz, J_{ac}=8.5 Hz, 1H), 6.08 (s, 2H), 4.23 (q, J=7.2 Hz, 2H), 1.21 (t, J=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.5, 165.1, 152.4, 148.3, 143.5, 143.2, 135.5, 131.9, 131.3, 129.6, 128.7, 127.6, 126.6, 122.9, 108.3, 108.1, 102.0, 61.2, 14.1. IR (neat) cm^{-1}: 2979, 2909, 1715, 1648, 1612, 1600, 1590, 1502, 1487, 1439, 1248. HRMS (m/z): calcd for $C_{21}H_{19}O_5$ [M−H$^+$], 351.1227; found, 351.1236. J_{C-H}: 8.1 Hz.

5.5.14. 2-(Benzo[1,3]dioxole-5-carbonyl)-hept-2-enoic acid ethyl ester (**26a**)

The intermediate isoxazoline (*5-benzo[1,3]dioxol-5-yl-3-butyl-2-methyl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure B (72% yield). ^{1}H NMR (400 MHz $CDCl_3$): δ 7.42 (d, J=8 Hz, 1H), 7.36 (s, 1H), 6.84 (d, J=8.4 Hz, 1H), 6.01 (s, 2H), 4.18 (m, 2H), 3.98 (m, 1H), 2.84 (s, 3H), 1.32–1.77 (m, 6H), 1.27 (t, J=7.2 Hz, 3H), 0.82 (t, J=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 160.9, 149.7, 147.0, 124.8, 121.1, 110.0, 107.7, 101.9, 101.4, 73.2, 59.8, 46.9, 34.4, 27.6, 22.5, 14.1, 13.9. IR (neat) cm^{-1}: 2979, 2902, 1697, 1627, 1600, 1504, 1488, 1448, 1332, 1251, 1226, 1130, 1108, 1039, 968, 933, 813, 761. HRMS (m/z): calcd for $C_{18}H_{24}NO_5$ [M−H$^+$], 334.1653; found, 334.1655.

General procedure C provided the title compound (**26a**) from the intermediate isoxazoline (95% combined yield with **26b**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.41 (m, 2H), 7.11 (t, J=8.0 Hz, 1H), 6.82 (d, J=8.0 Hz, 1H), 6.05 (s, 2H), 4.17 (q, J=7.2 Hz, 2H), 2.10 (q, J=7.5, 2H), 1.43–1.20 (m, 4H), 1.18 (t, J=7.5 Hz, 3H), 0.82 (t, J=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.6, 164.5, 152.3, 148.3, 147.9, 133.6, 131.8, 126.3, 108.2, 108.0, 101.9, 61.0, 30.4, 29.3, 22.3, 14.0, 13.7. IR (neat) cm^{-1}: 2957, 2930, 2905, 2861, 1711, 1663, 1602, 1503, 1487, 1439, 1366. HRMS (m/z): calcd for $C_{17}H_{21}O_5$ [M−H$^+$], 305. 1384; found, 305.1388. J_{C-H}: 7.3 Hz.

5.5.15. 2-(Benzo[1,3]dioxole-5-carbonyl)-acrylic acid ethyl ester (**27**)

The intermediate *N*-methyl isoxazoline (*5-benzo[1,3]dioxol-5-yl-2-methyl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure B (85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J=8 Hz, 1H), 7.38 (s, 1H), 6.84 (d, J=8 Hz, 1H), 6.00 (s, 2H), 4.58 (m, 1H), 4.21 (q, J=7 Hz, 2H), 3.96 (m, 1H), 2.87 (s, 3H), 1.28 (t, J=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 161.1, 149.7, 147.1, 124.6, 120.7, 109.8, 107.7, 101.4, 98.0, 62.5, 59.9, 47.5, 14.2. IR (neat) cm^{-1}: 3085, 2979, 2960, 2902, 2875, 2781. HRMS: calcd for $C_{14}H_{16}NO_5$ [M−H$^+$], 278.1023; found, 278.1031.

Alternatively, the intermediate *N-tert*-butyl isoxazoline (*5-benzo[1,3] dioxol-5-yl-2,3,3-trimethyl-2,3-dihydro-isoxazole-4-carboxylic acid ethyl ester*) was prepared according to general procedure B (79% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, J_{ab}=8 Hz, J_{ab}=1 Hz, 1H), 7.12 (d, J=1 Hz, 1H), 5.99 (s, 2H), 4.16 (q, J=7 Hz, 2H), 2.77 (s, 3H), 1.42 (s, 6H), 1.20 (t, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 161.7, 149.5, 147.0, 124.3, 121.9, 109.8, 107.7, 107.4, 101.4, 69.9, 59.6, 53.4, 38.4, 14.05. IR (neat) cm^{-1}: 2975, 2929, 2902, 1689, 1604, 1504, 1488, 1446, 1371. HRMS: calcd for $C_{16}H_{20}NO_5$ [M−H$^+$], 306.1336; found, 306.1344.

General procedure C provided the title compound (**27**) from either the *N*-methyl or *N-tert*-butyl intermediate isoxazoline. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (m, 2H), 6.87 (d, J=8.0 Hz, 1H), 6.66 (s, 1H), 6.08 (s, 2H), 6.00 (s, 1H), 4.28 (q, J=7.0 Hz, 2H), 1.25 (t, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 164.3, 152.3, 148.2, 141.3, 131.0, 130.4, 126.6, 108.6, 107.8, 101.9, 61.4, 13.9. IR (neat) cm^{-1}: 2981, 2897, 1718, 1661, 1603, 1502, 1487, 1439, 1392, 1367, 1354, 1316, 1248, 1219, 1092. HRMS: calcd for $C_{13}H_{13}O_5$ [M−H$^+$], 249.0758; found, 249.0753.

5.5.16. 2-(Benzo[1,3]dioxole-5-carbonyl)-3-methyl-but-2-enoic acid ethyl ester (**28**)

The intermediate isoxazoline (*5-benzo[1,3] dioxol-5-yl-2,3,3-trimethyl-2,3-dihydro-isoxazole-4-carbxylic acid ethyl ester*) was prepared by method B (0.248 g, 79%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, J_{ab}=8 Hz, J_{ab}=1 Hz, 1H), 7.12 (d, J=1 Hz, 1H), 5.99 (s, 2H), 4.16 (q, J=7 Hz, 2H), 2.77 (s, 3H), 1.42 (s, 6H), 1.20 (t, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 161.7, 149.5, 147.0, 124.3, 121.9, 109.8, 107.7, 107.4, 101.4, 69.9, 59.6, 53.4, 38.4, 14.05. IR (neat) cm^{-1}: 2975, 2929, 2902, 1689, 1604, 1504, 1488, 1446, 1371. HRMS: calcd for $C_{16}H_{20}NO_5$ [M−H$^+$], 306.1336; found, 306.1344.

General procedure C provided the title compound (**28**) from the intermediate isoxazoline. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (dd, J_{ab}=8.0 Hz, J_{ac}=1.2 Hz, 1H), 7.42 (d, J=1.2 Hz, 1H), 6.84 (d, J=8.0 Hz, 2H), 6.06 (s, 2H), 4.11 (d, J=7.0 Hz, 2H), 2.30 (s, 3H), 1.79 (s, 3H), 1.09 (t, J=8.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 164.7, 153.9, 152.1, 148.3, 132.0, 129.3, 125.9, 108.2, 108.0, 101.9, 60.4, 24.1, 22.1, 13.9. IR (neat) cm^{-1}: 2979, 2899, 1714, 1661, 1601, 1503, 1485, 1436, 1366, 1354, 1281, 1223. HRMS: calcd for $C_{15}H_{17}O_5$ [M−H$^+$], 277.1071; found, 277.1070.

*5.5.17. α-[(2E)-2-Methyl-3-phenyl-2-propen-1-ylidene]-β-oxo-3,5-bis[[tris(1-methylethyl)silyl]oxy]-, (αZ) benzenepropanoic acid methyl ester (**29b**)*

Alkynyl ester **9a** was subjected to general procedure D using the nitrone **10d** to yield 3.0 g (65%) of **29b**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, J=0.8 Hz, 1H), 7.34 (m, 5H), 7.07 (d, J=2.4 Hz, 2H), 6.98 (s, 1H), 6.65 (t, J=2.0 Hz, 1H), 3.69 (s, 3H), 1.79 (s, 3H), 1.24 (m, 6H), 1.12 (d, J=9.0 Hz, 36H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.0, 165.8, 157.3, 147.8, 141.9, 138.9, 136.2, 133.3, 129.7, 129.2, 128.3, 128.0, 117.3, 113.7, 52.3, 17.8, 12.5. IR (neat, cm^{-1}): 3024, 2945, 2892, 1724, 1714, 1679, 1672, 1588, 1443, 1334, 1249, 1198. HRMS (EI) calculated for $C_{38}H_{58}O_5Si_2$ 650.3817; found, 650.3817. $^3J_{C-H}$=4.2 Hz for C_{ketone}–H, $^3J_{C-H}$=7.5 Hz for C_{ester}–H.

*5.5.18. β-Oxo-α-[(2E)-3-phenyl-2-propen-1-ylidene]-3,5-bis[[tris(1-methylethyl)silyl]oxy]-, (αE) benzenepropanoic acid methyl ester (**30a**)*

Alkynyl ester **9a** (0.8 g, 1.5 mmol) was subjected to general procedure D using the nitrone **10c** to yield 320 mg (67%) of **30a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J=12.0 Hz, 1H), 7.34 (m, 5H), 7.05 (d, J=2.5 Hz, 2H), 7.02 (d, J=16.0 Hz, 1H), 6.70 (dd, J=2.5 Hz, 3.0 Hz, 1H), 6.66 (t, J=2.4 Hz, 1H), 3.71 (s, 3H), 1.26 (m, 6H), 1.10 (d, J=8.5 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 176.6, 165.4, 157.4, 143.6, 143.4, 138.7, 135.5, 131.0, 129.6, 128.7, 127.6, 123.0, 117.5, 113.9, 52.2, 17.8, 12.6. IR (neat, cm^{-1}): 2944, 2866, 1719, 1672, 1584, 1462, 1438, 1279, 1171. HRMS (EI) calculated for $C_{37}H_{56}O_5Si_2Na$: 659.3558; found, 659.3542. $^3J_{C-H}$=9.0 Hz for C_{ketone}–H, $^3J_{C-H}$=6.6 Hz for C_{ester}–H.

*5.5.19. N,N-Dimethyl-α-[(2E)-2-methyl-3-phenyl-2-propen-1-ylidene]-β-oxo-3,5-bis[[tris(1-methylethyl)silyl]oxy]-, (αZ) benzenepropanamide (**31b**)*

Alkynyl amide **9b** (1.6 g, 2.8 mmol) was subjected to general procedure D using the nitrone **10d** to obtain 1.2 g (63%) of **31b**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 (m, 5H), 7.02 (s, 1H), 6.88 (d, J=2.4 Hz, 2H), 6.79 (s, 1H), 6.62 (t, J=2.0 Hz, 1H), 3.08 (s, 3H), 3.01 (s, 3H), 2.08 (s, 3H), 1.24 (m, 6H), 1.10 (d, J=9.0 Hz, 36H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.2, 168.0, 156.9, 147.9, 141.5, 139.4, 136.3, 134.4, 133.7, 129.5, 128.3, 128.1, 115.5, 113.9, 38.2, 34.6, 17.8, 14.6, 12.6. IR (neat, cm^{-1}): 2945, 2867, 1643, 1585, 1437, 1393, 1336, 1239, 1072. HRMS (EI) calculated for $C_{39}H_{61}NO_4Si_2Na$ 686.4031; found, 686.4056. $^3J_{C-H}$=2.5 Hz for C_{ketone}–H, $^3J_{C-H}$=10.5 Hz for C_{ester}–H.

*5.5.20. P-[(1Z,3E)-1-[3,5-Bis[[tris(1-methylethyl)silyl]oxy]benzoyl]-3-methyl-4-phenyl-1,3-butadien-1-yl]-, phosphonic acid diethyl ester (**32b**)*

Alkynyl phosphate **9c** (2.7 g, 4.5 mmol) was subjected to general procedure D using the nitrone **10d** to obtain 1.9 g (57%) of **32b**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, J=26.0 Hz, 1H), 7.27 (m, 5H), 7.11 (d, J=2.0 Hz, 2H), 6.87 (s, 1H), 6.64 (t, J=2.0 Hz, 1H), 4.13 (quint., J=7.2 Hz, 4H), 1.75 (s, 3H), 1.24 (m, 12H), 1.12 (d, J=9.0 Hz, 36H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.0, 157.2, 155.9, 151.2, 140.4, 139.0, 136.2, 133.8, 133.6, 129.3, 128.2, 127.9, 117.3, 114.3, 114.0, 62.6, 17.8, 16.1, 12.5. IR (neat, cm^{-1}): 2868, 2728, 2359, 1666, 1587, 1445, 1334, 1173, 1027. HRMS (EI) calculated for $C_{40}H_{65}O_6PSi_2Na$ 751.3950; found, 751.3964. $^3J_{C-H}$=7.8 Hz for C_{ketone}–H.

*5.5.21. α-[(2E)-2-Methyl-3-phenyl-2-propen-1-ylidene]-β-oxo-3,5-bis[[tris(1-methylethyl)silyl]oxy]-, (αE) benzenepropanenitrile (**33b**)*

Alkynyl nitrile **9d** (2.4 g, 5.1 mmol) was subjected to general procedure D using the nitrone **10d** to obtain 1.8 g (57%) of **33b**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (s, 1H), 7.41 (m, 5H), 7.09 (s, 1H), 6.90 (d, J=2.0 Hz, 2H), 6.65 (t, J=2.0 Hz, 1H), 2.50 (s, 3H), 1.24 (m, 6H), 1.10 (d, J=9.0 Hz, 36H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.6, 160.3, 157.2, 147.5, 137.7, 135.4, 133.8, 130.0, 129.3, 128.6, 116.5, 113.7, 109.5, 17.9, 15.6, 12.6. IR (neat, cm^{-1}): 2943, 2866, 2210, 1555, 1581, 1435, 1172, 1030. HRMS (EI) calculated for $C_{37}H_{55}NO_3Si_2$ 617.3715; found, 617.3743. $^3J_{C-H}$=6.0 Hz for C_{ketone}–H, $^3J_{C-H}$=13.4 Hz for C_{ester}–H.

*5.5.22. 1-[3,5-Bis[[tris(1-methylethyl)silyl]oxy]phenyl]-4-methyl-2-[(4-methylphenyl)sulfonyl]-5-phenyl-, (2Z,4E) 2,4-pentadien-1-one (**34b**)*

Alkynyl sulfone **9e** (739 mg, 1.2 mmol) was subjected to general procedure D using the nitrone **10d** to obtain 191 mg (43%) of **34b**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, J=8.0 Hz, 2H), 7.69 (d, J=0.5 Hz, 1H), 7.30 (m, 5H), 7.17 (d, J=8.0 Hz, 2H), 7.03 (d, J=2.0 Hz, 2H), 6.92 (s, 1H), 6.64 (t, J=2.0 Hz, 1H), 2.42 (s, 3H), 1.68 (s, J=1.0 Hz, 3H), 1.24 (m, 6H), 1.10 (d, J=9.0 Hz, 36H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.6, 176.5, 157.3, 145.8, 144.4, 142.5, 139.0, 138.2, 137.3, 135.7, 131.9, 130.2, 129.6, 129.0, 128.3, 128.1, 117.8, 114.2, 21.6, 17.4, 16.2, 12.5. IR (neat, cm^{-1}): 2948, 2729, 1746, 1666, 1453, 1244, 1087. HRMS (EI) calculated for $C_{43}H_{62}O_5SSi_2Na$ 769.3749; found, 769.3740. $^3J_{C-H}$=8.8 Hz for C_{ketone}–H.

*5.5.23. 2-Benzylidene-1-phenyl-heptane-1,3-dione (**36b**)*

The intermediate *N*-methyl isoxazoline (*5-butyl-2-methyl-3-phenyl-2,3-dihydro-isoxazol-4-yl)-phenyl-mathanone*) was prepared according to general procedure A. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 2H), 7.53–7.23 (m, 8H), 5.27 (s, 1H), 2.96 (s, 3H), 2.22 (t, J=7 Hz, 2H), 1.55 (m, 2H), 1.22 (m, 2H), 0.80 (t, J=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 166.0, 141.0, 140.5, 140.2, 131.4, 128.4, 128.2, 127.7, 127.4, 127.2, 114.1, 77.1, 47.1, 28.9, 26.5, 22.2, 13.5. IR (neat) cm^{-1}: 2958, 2931, 1612, 1577, 1450, 1361, 1230, 1157. HRMS: calcd for $C_{21}H_{23}O_2N$ [M$^+$], 321.1723; found, 321.1717.

The intermediate *N-tert*-butyl isoxazoline (*5-butyl-2-tert-butyl-3-phenyl-2,3-dihydro-isoxazol-4-yl)-phenyl-mathanone)* was prepared according to general procedure A. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.39 (m, 5H), 7.35 (m, 2H), 2.26 (m, 2H), 7.20 (m, 1H), 5.64 (s, 1H), 5.29 (s, 1H), 2.15 (t, J=8 Hz, 2H), 1.53 (m, 2H), 1.27 (m, 3H), 1.18 (s, 9H), 1.88 (t, J=8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 166.0, 143.5, 140.4, 131.2, 128.28, 128.21, 127.6, 127.5, 127.1, 115.5, 68.9, 61.2, 29.1, 26.5, 24.9, 22.4, 13.5. IR (neat) cm^{-1}: 2974, 2958, 2928, 2873, 2857, 1633, 1595, 1574, 1494, 1457, 1447, 1371, 1363. HRMS: calcd for $C_{24}H_{30}O_2N$ [M−H$^+$], 364.2271; found, 364.2260.

General procedure C provided the title compound (**36b**) from the *N-tert*-butyl intermediate isoxazoline (61% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (m, 2H), 7.80 (m, 1.6H), 7.61–7.21 (m, 15H), 2.66 (t, J=7.0 Hz, 2H), 2.60 (t, J=7.0 Hz, 0.7H), 1.64 (m, 4.2H), 1.34 (m, 4.5H), 0.90 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 198.0, 141.8, 140.2, 139.4, 136.1, 134.5, 134.0, 133.0, 132.6, 130.4, 130.3, 130.2, 129.8, 129.5, 129.1, 128.95, 128.91, 128.7, 128.5, 127.9, 43.9, 39.3, 26.1, 25.3, 22.2, 22.0, 13.85, 13.81. IR (neat) cm^{-1}: 3060, 3029, 2919, 1706, 1700, 1640, 1609, 1598, 1449, 1320. HRMS: calcd for $C_{20}H_{21}O_2$ [M−H$^+$]; 293.1562; found, 293.1569.

*5.5.24. 2-Cyclohexylmethylene-1-phenyl-heptane-1,3-dione (**37a**)*

The intermediate *N*-methyl isoxazoline ((*5-butyl-3-cyclohexenyl-2-methyl-2,3-dihydro-isoxazol-4-yl)-phenyl-mathanone*) was prepared according to general procedure A (96% yield). ^{1}H NMR

(400 MHz, $CDCl_3$): δ 7.62 (m, 2H), 7.51 (m, 1H), 7.43 (m, 2H), 4.06 (d, J=4 Hz, 1H), 2.79 (s, 3H), 2.07 (m, 2H), 1.71–1.61 (m, 8H), 1.40 (m, 2H), 1.23–1.10 (m, 7H), 0.74 (t, J=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 166.1, 140.4, 131.2, 128.1, 127.7, 110.8, 77.7, 48.3, 41.5, 29.4, 28.8, 27.1, 26.2, 26.1, 25.9, 22.0, 13.3. IR (neat) cm^{-1}: 2923, 2850, 1608, 1573, 1446, 1357, 1242. HRMS: calcd for $C_{21}H_{30}O_2N$ [M−H$^+$]; 328.2271; found, 328.2278.

The intermediate *N-tert*-butyl isoxazoline ((*5-butyl-2-tert-butyl-3-cyclohexyl-2,3-dihydro-isoxazol-4-yl)-phenyl-mathanone*) was prepared according to general procedure A (83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (m, 2H), 7.48 (m, 1H), 7.41 (m, 2H), 4.45 (d, J=3.5 Hz, 1H), 2.03 (m, 2H), 1.72–1.38 (m, 9H), 1.25–1.12 (m, 18H), 0.72 (t, J=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.0, 167.9, 140.8, 131.1, 128.2, 113.1, 68.4, 60.6, 43.4, 29.8, 29.0, 27.8, 26.53, 26.51, 26.4, 25.1, 22.5, 13.4. IR (neat) cm^{-1}: 2983, 2959, 2917, 2849, 1630, 1595, 1577, 1460, 1444, 1376, 1364, 1298, 1234, 1204, 1172. HRMS: calcd for $C_{24}H_{36}NO_2$ [M−H$^+$], 370.2741; found, 370.2756.

General procedure C provided the title compound (**37a**) from the *N-tert*-butyl intermediate isoxazoline (66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, J_{ab}=7.0 Hz, J_{ac}=5.0 Hz, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 6.25 (d, J=10.0 Hz, 1H), 2.61 (t, J=7.0 Hz, 1H), 1.80–1.56 (m, 8H), 1.34–1.11 (m, 7H), 0.88 (t, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 195.4, 154.5, 140.6, 137.4, 132.7, 129.5, 128.5, 43.4, 38.6, 32.1, 25.7, 25.6, 25.1, 22.1, 13.8. IR (neat) cm^{-1}: 3060, 3029, 2932, 2856, 1709, 1700, 1657, 1652, 1613, 1450. HRMS: calcd for $C_{20}H_{26}O_2$ [M−H$^+$]; 298.1927; found, 298.1939.

*5.5.25. 1-Phenyl-2-(3-phenyl-allylidene)-heptane-1,3-dione (**38**)*

The intermediate isoxazoline *(5-butyl-2-tert-butyl-3-styryl-2,3-dihydro-isoxazol-4-yl)-phenyl-mathanone)* was prepared according to general procedure A (64% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (m, 2H), 7.49 (m, 1H), 7.42 (m, 2H), 7.36 (M, 2H), 7.26 (m, 2H), 7.20 (m, 1H), 6.56 (d, J=16 Hz, 1H), 6.34 (dd, J_{ab}=16 Hz, J_{ac}=6.5 Hz, 1H), 5.36 (d, J=6.5 Hz, 1H), 2.14 (m, 2H), 1.52–1.44 (m, 2H), 1.22 (m, 11H), 0.79 (t, J=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.8, 166.9, 140.6, 136.9, 131.3, 130.5, 129.6, 129.5, 128.8, 128.5, 128.39, 128.32, 128.0, 127.7, 127.3, 126.6, 113.2, 67.0, 60.9, 29.0, 26.6, 25.0, 22.4, 13.5. IR (neat) cm^{-1}: 3024, 2959, 2931, 2870, 1597, 1574, 1446, 1359, 1228, 1209, 1191. HRMS: calcd for $C_{26}H_{32}NO_2$ [M−H$^+$], 390.2428; found, 390.2424.

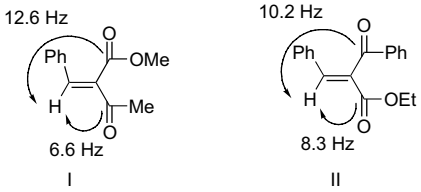
General procedure C provided the title compounds (**38a** and **38b**) as a mixture of isomers (7:1) from the intermediate isoxazoline (63% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, J=7.0 Hz, 0.49H), 7.62 (d, J=7.0 Hz, 2H), 7.59–7.26 (m, 15H), 7.01 (m, 2.43H), 6.69 (m, 0.22H), 2.64 (m, 2.63H), 1.63 (m, 3.18H), 1.32 (m, 4.02H), 0.89 (m, 4.37H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.3, 198.1, 196.9, 195.5, 145.7, 145.5, 144.0, 141.2, 139.5, 139.0, 137.7, 137.1, 135.7, 135.5, 134.5, 133.9, 1328, 129.9, 129.7, 129.4, 129.3, 128.9, 128.8, 127.9, 127.6, 123.8, 123.3, 77.2, 43.1, 39.4, 30.3, 26.2, 26.1, 22.3, 22.2, 13.8. IR (neat) cm^{-1}: 3060, 3029, 2932, 2856, 1709, 1700, 1657, 1652, 1613, 1575, 1449. HRMS: calcd for $C_{22}H_{22}O_2$ [M$^+$], 318.1614; found, 318.1612.

5.6. Assignment of olefin geometry for β-ketoalkylidene compounds

Product geometries were assigned based on carbon–hydrogen coupling constants obtained for the ester and/or the ketone of the divinyl ketone. A detailed study by Kingsbury gives tabulated splitting constants for a wide variety of differentially substituted olefins.[22]

As shown, $J^{13}_{\text{C–H ester}}$ (trans) couplings are on the order of ~12–13 Hz (I) and $J^{13}_{\text{C–H ketone}}$ (cis) couplings are on the order of ~6–7 Hz (I). $J^{13}_{\text{C–H ester}}$ (cis) couplings are on the order of ~8–9 Hz and $J^{13}_{\text{C–H ketone}}$ (cis) couplings are on the order of ~10–11 Hz. Because these coupling constants can be easily distinguished, either the $J^{13}_{\text{C–H ester}}$ or the $J^{13}_{\text{C–H ketone}}$ can be measured to assign olefin geometry, and in ambiguous cases both $J^{13}_{\text{C–H ketone}}$ and $J^{13}_{\text{C–H ester}}$ can be measured to clarify the hydrogen–carbonyl relationship.

Literature reports of ^{13}C-H coupling constants.



The above data (along with data previously tabulated within our group)[6b] assignments of product olefin geometry can be done with a high degree of confidence. All $J^{13}_{\text{C–H}}$ were obtained using $J^{13}_{\text{C–H ester}}$ with the exception of **15a**. In that particular case $J^{13}_{\text{C–H ketone}}$ was used.

5.7. Preparation of Baylis–Hillman adducts

5.7.1. 1-(2-tert-Butyl-3,5-diphenyl-2,3-dihydro-isoxazole-4-yl)-pentan-1-one (44)

Prepared by general procedure A. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.26 (m, 10H), 5.61 (s, 1H), 2.11 (t, J=7.2 Hz, 2H), 1.35 (m, 2H), 1.28 (s, 9H), 0.99 (m, 2H), 0.67 (t, J=7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 162.8, 143.4, 131.0, 129.3, 128.5, 128.48, 128.42, 127.5, 127.3, 116.6, 68.8, 61.5, 40.2, 26.6, 25.0, 22.0, 13.6. IR (neat) cm^{-1}: 3060, 3029, 2956, 2930, 2871, 1671, 1622, 1593, 1490, 1452, 1445, 1363, 1234, 1205, 1137. HRMS: calcd for $C_{24}H_{30}NO_2$ [M−H$^+$], 364.2271; found, 364.2265.

*5.7.2. 1-(2-tert-Butyl-3,5-diphenyl-2,3-dihydro-isoxazole-4-yl)-pentan-1-ol (**45**)*

$NaBH_4$ (0.010 g, 0.28 mmol) was added slowly to a stirred solution of isoxazoline **44** (0.100 g, 0.28 mmol) in MeOH (1 mL) at 0 °C. This was stirred for about 1 h, when it was quenched with H_2O (2 mL). This was extracted with Et_2O (3×5 mL), dried over $MgSO_4$ and concentrated to give pure products as a 2:1 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (m, 1.4H), 7.55 (m, 1H), 7.47–7.26 (m, 11.4H), 5.37 (s, 0.3H), 5.23 (0.7H), 4.56 (t, J=6.5 Hz, 0.3H), 4.41 (t, J=6.5 Hz, 0.7H), 1.67–1.60 (m, 2.1H), 1.35–1.18 (m, 9H), 0.89 (t, J=6.5 Hz, 3H), 0.78 (t, J=6.5 Hz, 1.1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 150.1, 145.0, 144.7, 131.0, 129.6, 129.4, 129.3, 129.2, 129.1, 128.8, 128.58, 128.53, 128.4, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 127.2, 127.0, 126.8, 126.7, 112.8, 111.6, 68.9 (2), 67.9 (2), 61.2, 61.0, 35.9, 30.3, 28.3, 26.1, 25.1, 22.6, 22.3, 22.2, 14.0. IR (neat) cm^{-1}: 3513, 3052, 3025, 2945, 2928, 2853, 1666, 1629, 1593, 1494, 1447, 1445, 1370, 1234, 1210, 1137. HRMS: calcd for $C_{18}H_{28}NO_2$ [M−H$^+$], 290.2115; found, 290.2120.

*5.7.3. 2-Benzylidene-3-hydroxy-1-phenyl-heptan-1-one (**46**)*[35]

Oxidized according to general procedure C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.02 (m, 11H), 4.80 (m, 1H), 3.89 (m, 1H), 1.94 (m, 1H), 1.72 (m, 1H), 1.48 (m, 1H), 1.34 (m, 3H), 0.877 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 142.7, 141.3, 137.9, 134.4, 132.7, 129.8, 129.2, 128.9, 128.6, 128.3, 70.0, 36.1, 28.4, 22.5, 14.0. IR (neat) cm^{-1}: 3413, 2956, 1650, 1595, 1447, 1377, 1229, 1070, 1001, 950.

*5.7.4. (5-Butyl-2-tert-butyl-3-phenyl-2,3-dihydro-isoxazol-4-yl)-phenyl-mathanone (**47**)*

Prepared according to general procedure A. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.39 (m, 5H), 7.35 (m, 2H), 2.26 (m, 2H), 7.20 (m, 1H),

5.64 (s, 1H), 5.29 (s, 1H), 2.15 (t, J=8.0 Hz, 2H), 1.53 (m, 2H), 1.27 (m, 3H), 1.18 (s, 9H), 1.88 (t, J=8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 166.0, 143.5, 140.4, 131.2, 128.28, 128.21, 127.6, 127.5, 127.1, 115.5, 68.9, 61.2, 29.1, 26.5, 24.9, 22.4, 13.5. IR (neat) cm^{-1}: 2974, 2958, 2928, 2873, 2857, 1633, 1595, 1574, 1494, 1457, 1447, 1371, 1363. HRMS: calcd for $C_{24}H_{30}O_2N$ [M−H$^+$], 364.2271; found, 364.2260.

*5.7.5. (5-Butyl-2-tert-butyl-3-phenyl-2,3-dihydro-isoxazol-4-yl)-phenyl-methanol (**48**)*

DIBAL (1.0 M/toluene, 0.21 mL) was added slowly to a stirred solution of isoxazoline **10f** (0.050 g, 0.14 mmol) in dichloromethane (0.28 mL) at 0 °C. This was stirred for about 10 min, quenched with MeOH (0.30 mL) and warmed to rt. The solid was filtered off, and the filtrate was concentrated. Column chromatography provided alcohol **47** (0.035 g, 73%) as a 3:1 mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.14 (m, 13H), 5.16 (m, 0.3H), 4.86 (m, 1H), 4.62 (s, 0.3H), 2.39 (m, 3H), 1.64–1.37 (m, 9.2H), 1.07 (s, 9H), 0.96 (m, 9.2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 151.9, 143.8, 142.1, 142.0, 128.8, 128.3, 128.1, 128.0, 127.65, 127.60, 127.2, 127.08, 127.01, 126.0, 125.5, 110.1, 109.6, 70.0, 69.9, 69.2, 68.1, 60.59, 60.53, 29.7, 29.6, 24.9, 24.7, 24.3, 22.79, 22.73, 13.8. IR (neat) cm^{-1}: 3346, 2962, 2957, 2928, 2877, 2863, 1587, 1571, 1488, 1457, 1444, 1378, 1362. HRMS: calcd for $C_{24}H_{32}NO_2$ [M−H$^+$], 366.2479; found, 366.2473.

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Supplementary data

^{1}H and ^{13}C spectra for all compounds can be found in the Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.003.

References and notes

1. (a) Thibonnet, J.; Vu, V. A.; Berillon, L.; Knochel, P. *Tetrahedron* **2002**, *58*, 4787; (b) Acuna, C.; Zapata, A. *Synth. Commun.* **1988**, *18*, 1133.
2. (a) Marino, J. P.; Lindermann, R. J. *J. Org. Chem.* **1981**, *46*, 3696; (b) Marino, J. P.; Lindermann, R. J. *J. Org. Chem.* **1983**, *48*, 4621; (c) Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* **2003**, 1380.
3. Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377.
4. Mazzola, R. D.; Giese, S.; Benson, C. L.; West, F. G. *J. Org. Chem.* **2004**, *69*, 220.
5. Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A.; Venturello, P. *J. Org. Chem.* **2002**, *67*, 7144.
6. (a) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278; addition/correction *J. Am. Chem. Soc.* **2004**, *126*, 10493; (b) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661.
7. (a) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 341; (b) Tanikaga, R.; Konya, N.; Hamamura, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3211; (c) Desimoni, G.; Faita, G.; Ricci, M.; Righetti, P. P. *Tetrahedron* **1998**, *54*, 9581.
8. (a) Padwa, A.; Kline, D. N.; Perumattam, J. *Tetrahedron Lett.* **1987**, *28*, 913; (b) Padwa, A.; Chiacchio, U.; Kline, D. N.; Perumattam, J. *J. Org. Chem.* **1988**, *53*, 2238; (c) According to the authors, only one product isomer was isolated, and the geometry drawn for the product would have arisen from 'outward' disrotation. The method used to assign the olefin geometry was not described.
9. (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Chemie: Weinheim, 1970; (b) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.
10. (a) Mock, W. L. *J. Am. Chem. Soc.* **1966**, *88*, 2857; (b) McGregor, S. D.; Lemal, D. M. *J. Am. Chem. Soc.* **1966**, *88*, 2858; (c) Lemal, D. M.; McGregor, S. D. *J. Am. Chem. Soc.* **1966**, *88*, 1335; (d) Mock, W. L. *J. Am. Chem. Soc.* **1975**, *97*, 3666.
11. (a) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099; (b) Doulbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471; (c) Lee, P. S.; Zhang, X. Y.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5072 and references therein; (d) Evanseck, J. D.; Thomas, B. E.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1995**, *60*, 7134; (e) For another study proposing a role for geminal bonds in the torquoselectivity of retroelectrocyclizations, see: Luo, L.; Bartberger, M. D.; Dolbier, W. J. *J. Am. Chem. Soc.* **1997**, *119*, 12366; (f) Yasui, M.; Naruse, Y.; Inagaki, S. *J. Org. Chem.* **2004**, *69*, 7246 and references therein.
12. For recent theoretical investigations of torquoselective Nazarov-type cyclizations, see: (a) Dieker, J.; Froehlich, R.; Wuerthwein, E.-U. *Eur. J. Org. Chem.* **2006**, *23*, 5339; (b) Cavalli, A.; Masetti, M.; Recanatini, M.; Prandi, C.; Guarna, A.; Occhiato, E. G. *Chem.—Eur. J.* **2006**, *12*, 2836; (c) Harmata, M.; Schreiner, P. R.; Lee, D. R.; Kirchhoefer, P. L. *J. Am. Chem. Soc.* **2004**, *126*, 10954; For a recent theoretical investigation of a torquoselective sigmatropic shift, see: (d) Faza, O. N.; Lopez, C. S.; de Lera, A. R. *J. Org. Chem.* **2007**, *72*, 2617; For recent theoretical investigations of torquoselective electrocyclic ring openings and closures, see: (e) Murakami, M.; Hasegawa, M.; Igawa, H. *J. Org. Chem.* **2004**, *69*, 587; (f) Walker, M. J.; Hietbrink, B. N.; Thomas, B. E., IV; Nakamura, K.; Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 6669; (g) Ikeda, H.; Kato, T.; Inagaki, S. *Chem. Lett.* **2001**, *3*, 270; (h) Murakami, M.; Miyamoto, Y.; Ito, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 189; For a recent theoretical investigation of a torquoselective Cope Rearrangement, see: Zhao, Y.-L.; Suhrada, C. P.; Jung, M. E.; Houk, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 11106.
13. Naruse, Y.; Hayashi, Y.; Inagaki, S. *Tetrahedron Lett.* **2003**, *44*, 8509.
14. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
15. Sai, H. *Synthesis* **1995**, 582.
16. Bolin, D. G.; Paquette, L. A.; Schulze, M. M. *J. Org. Chem.* **1994**, *59*, 2043.
17. Harding, K. E.; Ligon, R. C. *Synth. Commun.* **1974**, *4*, 297.
18. Chaidez, M. A.; Inman, W. D.; Paulson, D. R.; Sanchez, A. K. J. *J. Org. Chem.* **1989**, *54*, 4872.
19. Negishi, E.-i.; King, A. O.; Klima, W. L.; Patterson, W.; Silveira, A., Jr. *J. Org. Chem.* **1980**, *45*, 2526.
20. Nair, V.; Augustine, A.; Suja, T. D. *Synthesis* **2002**, *15*, 2259.
21. Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.
22. Kingsbury, C. A.; Draney, D.; Sopchik, A.; Rissler, W.; Durham, D. *J. Org. Chem.* **1976**, *41*, 3863.
23. (a) Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.* **1968**, *90*, 5325; (b) Adachi, I.; Harada, K.; Kano, H. *Tetrahedron Lett.* **1969**, *55*, 4875; (c) Ishikawa, T.; Kudoh, T.; Yoshida, J.; Yasuhara, A.; Manabe, S.; Saito, S. *Org. Lett.* **2002**, *4*, 1907.
24. (a) Merino, P.; Tejero, T.; Laguna, M.; Cerrada, E.; Moreno, A.; Lopez, J. A. *Org. Biomol. Chem.* **2003**, *1*, 2336; (b) Kanemasa, S.; Ueno, N.; Shirahase, M. *Tetrahedron Lett.* **2002**, *43*, 657 and references therein.
25. (a) Stang, P. J.; Murch, P. *Tetrahedron Lett.* **1997**, *38*, 8793; (b) Hems, W. P.; Tan, C.-H.; Stork, T.; Feeder, N.; Holmes, A. B. *Tetrahedron Lett.* **1999**, *40*, 1393; (c) Chermier, M.-O. J.; Moussalli, N.; Chanet-Ray, J.; Chou, S. *J. Chem. Res., Synop.* **1999**, 566.
26. (a) Hoffman, A. W. *Lieb. Ann.* **1851**, *78*, 253; (b) Hoffman, A. W. *Lieb. Ann.* **1851**, *79*, 11; (c) Hoffmann, A. W. *Berichte* **1881**, *14*, 659; (d) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317.
27. Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
28. Singh, V. K. *Synthesis* **1992**, 607.
29. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
30. Masamune, S.; Seidner, R. T.; Wilson, K. E. *J. Chem. Soc., Chem. Commun.* **1970**, 213.
31. For experimental data for compounds **49**, see: Trost, B. M.; Shuichi, O. *J. Am. Chem. Soc.* **2001**, *123*, 1230.
32. He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003.
33. (a) Chiacchio, U.; Liguori, A.; Rescifina, A.; Romeo, G.; Rossano, F.; Sindona, G.; Uccella, N. *Tetrahedron* **1992**, *48*, 123; (b) Chiacchio, U.; Casuscelli, F.; Liguori, A.; Romeo, G.; Sindona, G.; Uccella, N. *Heterocycles* **1993**, *36*, 585–600; (c) Casuscelli, F.; Chiacchio, U.; Rescifina, A.; Romeo, R.; Romeo, G.; Tommasini, S.; Uccella, N. *Tetrahedron* **1995**, *51*, 2979.
34. Canterbury, D. P.; Frontier, A. J.; Um, J. M.; Cheong, P. H.-Y.; Goldfeld, D. A.; Huhn, R. A.; Houk, K. N. *Org. Lett.*, **2008**, *10*, 4597.
35. Kazuhiro, Y.; Takayuki, S. *Tetrahedron* **2007**, *63*, 6259.