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# A Giese reaction for electron-rich alkenes†‡

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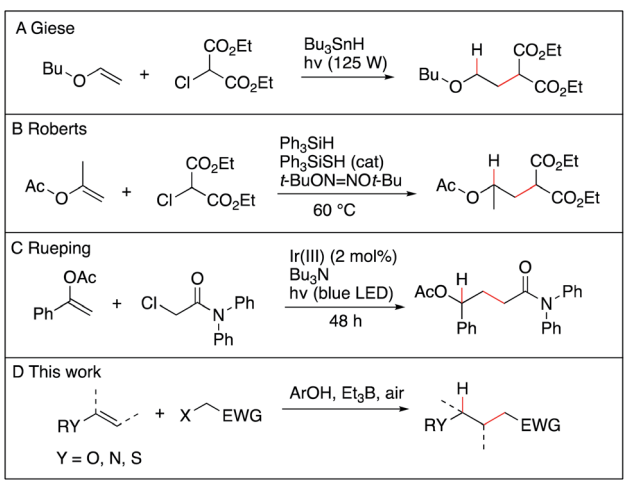
A general method for the hydroalkylation of electron-rich terminal and non-terminal alkenes such as enol esters, alkenyl sulfides, enol ethers, silyl enol ethers, enamides and enecarbamates has been developed. The reactions are carried out at room temperature under air initiation in the presence of triethylborane acting as a chain transfer reagent and 4-*tert*-butylcatechol (TBC) as a source of hydrogen atom. The efficacy of the reaction is best explained by very favorable polar effects supporting the chain process and minimizing undesired polar reactions. The stereoselective hydroalkylation of chiral *N*-(alk-1-en-1-yl)oxazolidin-2-ones takes place with good to excellent diastereocontrol.

## Introduction

The anti-Markovnikov selective hydroalkylation of heteroatom-substituted electron-rich alkenes such as enol esters, enol ethers, thioenol ethers and enamides is an attractive process for the preparation of a variety of functionalized building blocks used for the synthesis of natural products and analogues. The well-established transition metal catalyzed hydroformylation reaction represents an effective approach to introduce one carbon atom[1] and some promising results, such as the iridium catalyzed hydroalkylation of terminal alkenes with ureas,[2] may emerge in the future. However, a general solution allowing to introduce a broad range of functionalized alkyl groups remains still greatly needed. Radical chemistry has been proved during the last 40 years to be one of the mildest method to achieve C–C bond formation.[3–7] As for the hydroalkylation process, most of the reported methods described the addition of nucleophilic radicals to electron-poor olefins (the classical Giese reaction),[8–12] the reversed process, *i.e.*, addition of electrophilic radical to electron-rich olefins, remains scarce. The addition of diethyl chloromalonate to vinyl ethers and silyl enol ethers using tributyltin hydride as the hydrogen source was reported by Giese *et al.* (Scheme 1A),[13] followed a few years later by Renaud *et al.* who reported the hydroalkylation of enamines with sulfinylated and sulfonylated carbon-centered radicals in the presence of tributyltin hydride.[14–16] Examples of two-step procedures involving a xanthate group transfer reaction followed by a reduction step have been reported by Zard.[17,18] Roberts *et al.* reported triphenylsilane-mediated hydroalkylation of enol esters with electrophilic radicals in the presence of a thiol catalyst (Scheme 1B).[19] Recently, Ryu *et al.* reported the hydroalkylation of butyl vinyl ether with ethyl 2-bromoacetate using *in situ* generated HBr as a source of hydrogen atom.[20] Rueping *et al.* reported recently photoredox-catalyzed hydroalkylation of styrene derivatives and related olefins with α-halo amides (Scheme 1C)[21] that was later extended to cyclization of enamides.[22] These methods, however, suffer from serious limitations, such as limited scope, competing direct reduction of the halide, toxicity of reagents such as tin hydride, use of expensive catalyst, and long reaction time. The hydroalkylation of enol ethers, vinyl sulfides, and enamides with Markovnikov regioselectivity has been reported recently by Baran and Shenvi using an elegant metal-hydride hydrogen atom transfer process.[23–25] Developing a general, mild and environmentally friendly method for the hydroalkylation of electron-rich alkenes with anti-Markovnikov regioselectivity remains to date an unsolved problem.




Scheme 1 Hydroalkylation of electron-rich alkenes with anti-Markovnikov regioselectivity.

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† Dedicated with admiration and friendship to Professor Ilhyong Ryu for his 70th birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures and full characterization of all new compounds including copies of $^{1}$H- and $^{13}$C-NMR spectra. CCDC 2031378, 2031380 and 2031383. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc06341j

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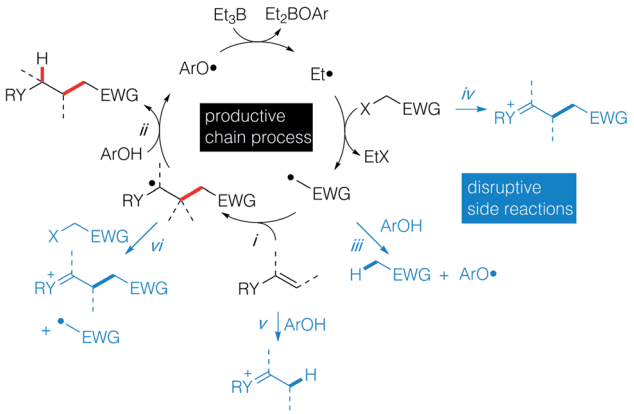



**Productive chain process**

*i* radical addition of EWG–C(•) to the e-rich alkene (favored by polar effects)
*ii* HAT from TBC to RY–C(•) (favored by polar effects)

**Potential disruptive side reactions**

*iii* direct HAT from TBC to EWG–C(•) (disfavored by polar effects)
*iv* ionic alkylation of the e-rich alkenes by the radical precursor (X = I)
*v* protonation of the e-rich alkene
*vi* SET between the e-rich radical RY–C(•) and the radical precursor (X = halide)

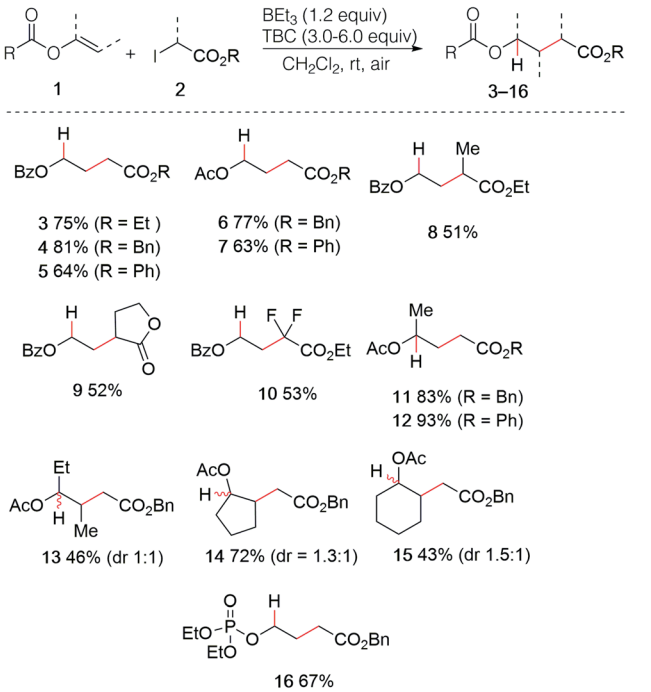
Scheme 2 Proposed strategy for a general approach to hydroalkylated electron-rich alkenes showing the productive chain process (in black) and potential disruptive side reactions (in blue).

Recently, we have reported the hydroalkylation of mono- and polysubstituted unactivated alkenes with activated alkyl iodides by using 4-*tert*-butylcatechol (TBC) as the hydrogen source and triethylborane as an initiator and chain transfer reagent.[26,27] The high efficiency of this reaction was attributed to strong polar effects, the catechol being a source of electrophilic hydrogen atoms, and to a unique repair mechanism, the system of catechol/$Et_3B$ being able to annihilate and repair undesired hydrogen atom transfer process involving the starting alkenes. Encouraged by these results, we decided to investigate the challenging hydroalkylation of electron-rich alkenes such as enol esters, enol ethers, enamides and related compounds. We described here a particularly general and simple approach to achieve this goal using TBC, a well-known biomimetic and non-toxic phenolic source of hydrogen atom (Scheme 1D). This reaction was expected to be strongly favored by polar effects since the electron-poor alkyl radicals add rapidly to the electron-rich alkenes (Scheme 2i). Moreover, the unique protic character of the OH group of TBC favors the fast reduction of the electron-rich radical adducts (Scheme 2ii) and disfavors the reduction of the initial electrophilic radicals (Scheme 2iii). Potential undesired chain disruptive side reactions such as ionic alkylations, protonation of the electron-rich alkenes (Scheme 2iv and v), and single electron transfer (SET) between the electron-rich radical adduct and the starting radical precursor (Scheme 2vi) do not take place under our reaction conditions.

## Results and discussion

### Hydroalkylation of enol esters and alkenyl sulfides

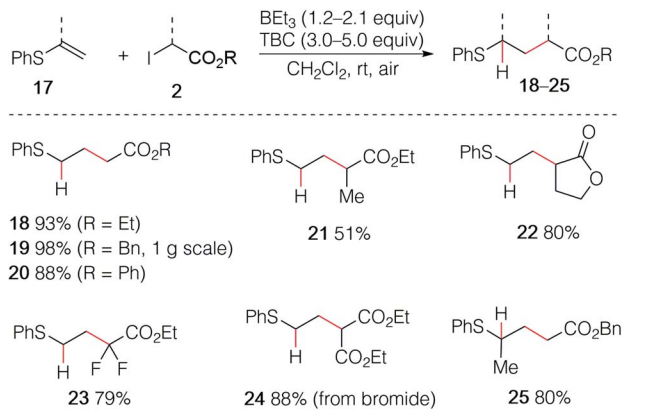
The use of enol esters was tested first. Simple mixing vinyl benzoate (5.0 equiv.), ethyl iodoacetate (1.0 equiv.), TBC (3.0 equiv.) and triethylborane (1 M in hexane, 1.2 equiv.) in



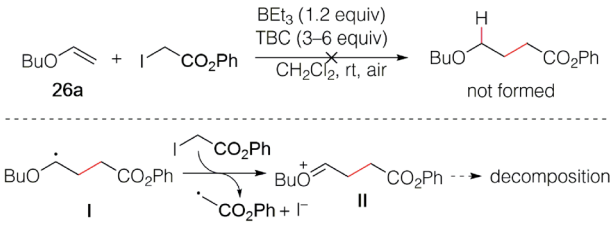

Scheme 3 Radical hydroalkylation of enol esters and vinyl phosphate.

dichloromethane under nitrogen atmosphere followed by stirring the reaction mixture open to air afforded the desired hydroalkylated product **3** in 75% yield (Scheme 3). Various di- and trisubstituted enol esters were tested using different electrophilic radical precursors. The method worked efficiently with terminal (**3–12**) as well as non-terminal enol esters (**13–15**) and can be also extended to the phosphate ester (**16**). A broad range of 2-iodoesters such as simple iodoacetates (**3–7**, **11–16**), 2-iodopropionates (**8**), the iodolactone (**9**) and the difluoroiodoacetate (**10**) were all found to react cleanly under these reaction conditions.

The reaction was then extended with success to alkenyl sulfides **17**, affording the corresponding sulfides **18–25** in good to excellent yields (Scheme 4). The sulfide **19** was easily prepared by using this procedure on gram scale. Interestingly,




Scheme 4 Hydroalkylation of alkenyl sulfides.



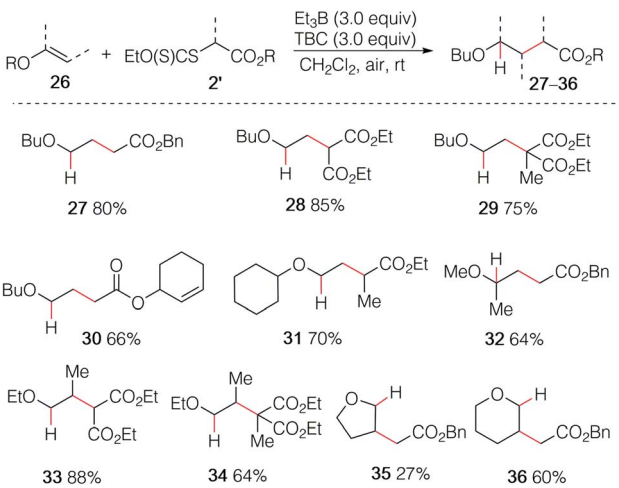

Scheme 5 Reaction of phenyl iodoacetate with butyl vinyl ether.

the diethyl malonate derivative **24** was prepared in high yield using the corresponding bromomalonate radical precursor.

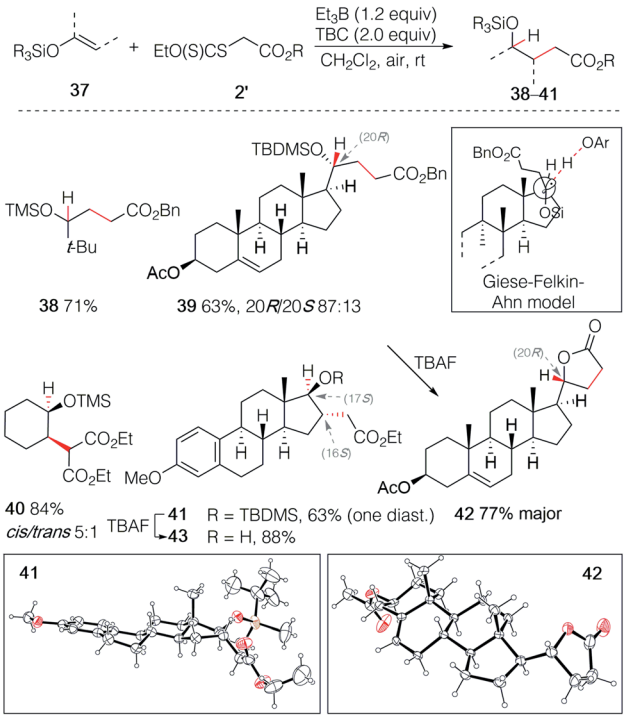
### Hydroalkylation of enol ethers

The reaction of butyl vinyl ether (**26a**) and phenyl iodoacetate was then attempted but led to decomposition products (Scheme 5). This was attributed to a fast electron transfer between radical adduct **I** and the starting iodoester **2c**, leading to the formation of the oxonium ion **II** that decomposes presumably by oligomerization processes involving the starting vinyl ether. Similar reactions have been reported by Giese in his seminal work.[13]

By employing xanthate radical precursors **2′** that are less prone to single electron transfer reduction than iodides,[18,28–30] the hydroalkylation of enol ethers **26** could be successfully performed (Scheme 6). For instance, reaction of vinyl ethers with various xanthates afforded the hydroalkylated products **27–31** in 70–85% yield. Noteworthy, the reaction between the unsaturated cyclohex-2-en-1-yl acetate xanthate and butyl vinyl ethers **26a** led to product **30** resulting from intermolecular addition in 66% yield, while no cyclized product was detected.[31] Similar result was obtained for **32** starting from 2-methoxypropene. Interestingly, non-terminal 1-ethoxypropene also reacted efficiently to deliver the corresponding adducts **33** and **34** in 88% and 64% yield, respectively. Cyclic enol ethers such as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran did not react cleanly at room temperature and better results were obtained by running the reaction at 0 °C (**35** 27%, **36** 60%).

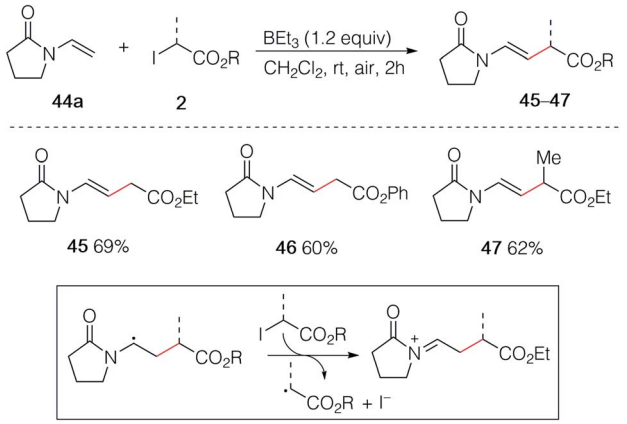



Scheme 6 Radical hydroalkylation of enol ethers with xanthates.




Scheme 7 Radical hydroalkylation of silyl enol ethers with xanthates. Single crystal X-ray structures of **42** and **43** (ellipsoids drawn at 50% probability).

The hydroalkylation of terminal silyl enol ethers was examined next. Terminal silyl enol ethers derived from *tert*-butyl methyl ketone and pregnenolone acetate gave the desired γ-silyloxy esters **38** and **39** in 71% and 63% yield, respectively (Scheme 7). The silyl ether **39** was obtained with a good control of the stereochemistry (20*R*/20*S* 87 : 13). The stereochemical outcome is rationalized by the Felkin–Ahn type model introduced by Giese for 1-alkoxysubstituted radicals.[32] This example illustrates also the high regioselectivity of this hydroalkylation process. Indeed, the double bond in ring B of pregnenolone that can be hydroalkylated in 65% yield under similar reaction conditions[26] remains untouched, demonstrating further the critical importance of polar effects in this reaction. Upon deprotection of the *tert*-butyldimethylsilyl (TBDMS) ether with TBAF, spontaneous lactonization affording **42** was observed. The major diastereomer of **42** was obtained in 77% yield and its (*R*) configuration at C(20) was confirmed by single crystal X-ray crystallography (Scheme 7).[33–37] Similar results were obtained with the non-terminal silyl enol ethers derived from cyclohexanone and estrone methyl ether that gave the γ-silyloxy esters **40** and **41** in 84% (*cis*/*trans* mixture 5 : 1) and 59% (single diastereomer) yield, respectively. The relative configuration at C(16) and C(17) of **41** was established by single crystal X-ray crystallography (Scheme 7),[33–37] indicating that both the stereochemical outcome of the radical addition and of the hydrogen atom transfer are controlled by the axial C(18)-methyl group. Deprotection of the silyl ether of **41** gave the stable *trans*-γ-hydroxy ester **43** and no lactonization could be achieved even under acidic treatment. Interestingly, the hydroalkylation of $Me_3SiO$-




Scheme 8 Non-reductive alkylation of 1-vinylpyrrolidin-2-one **44a** with iodoesters **2**.

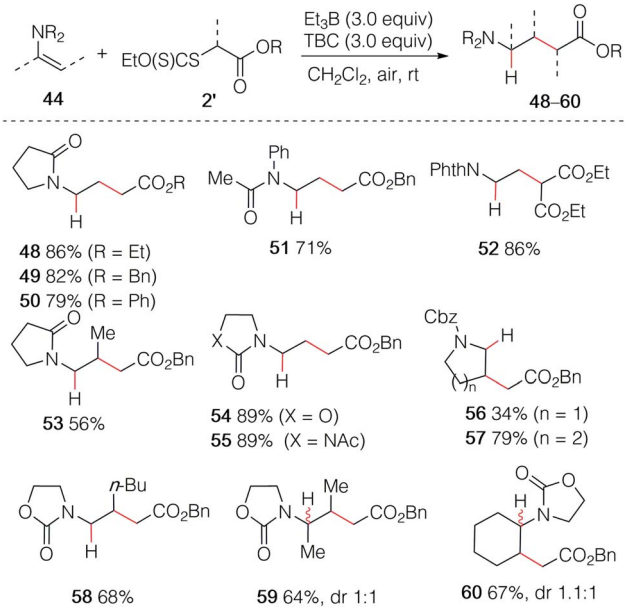
cyclohexene reported by Baran and co-workers[23,24] using an iron catalyzed process and by Shenvi using a dual manganese/nickel catalyzed process delivered adducts with the opposite regioselectivity.[25]

### Hydroalkylation of enamides and enecarbamates

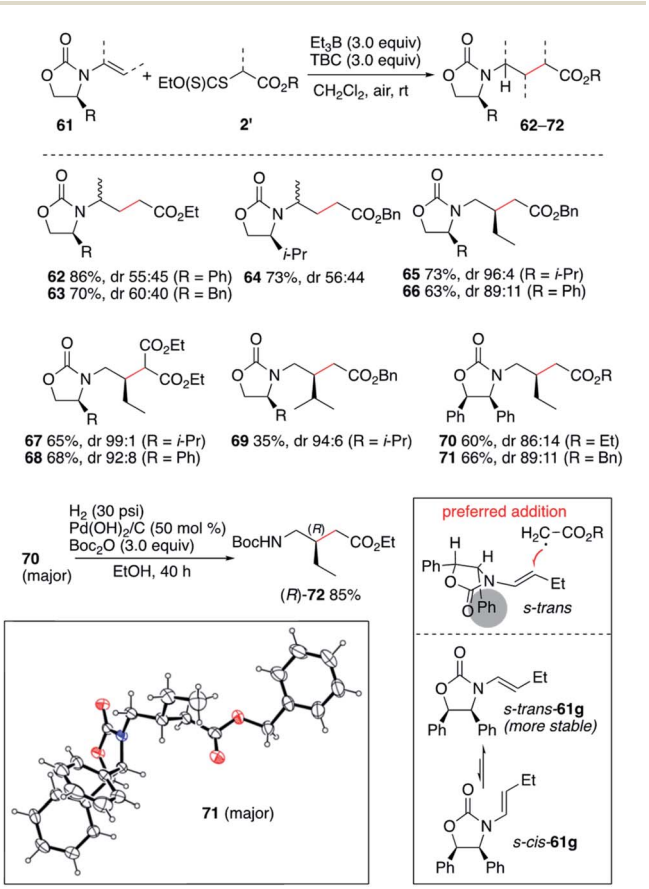
In an early attempt to run the hydroalkylation of 1-vinylpyrrolidin-2-one (**44a**) using ethyl iodoacetate, no trace of the hydroalkylated product was observed. Instead, the alkylated enamide **45** resulting from a non-reductive process was isolated. Rapid optimization of this process showed, as expected, that TBC was not necessary for this transformation and good yields of **45**, **46** and **47** were obtained upon simple treatment of **44a** with the correspond α-iodoesters in the presence of triethylborane which is presumably acting as a radical initiator in the presence of air and as a scavenger for HI generated during the process (Scheme 8). A similar non-reductive alkylation has already been reported by Friestad and Wu but required the use of a stoichiometric amount of tin hydride and a tertiary amine base.[38] The reaction proceeds *via* formation of an acyliminium ion resulting most probably from a single electron transfer process between the radical adduct and the starting iodide **2** followed by elimination of a proton (Scheme 8, frame).[39]

As already demonstrated for the enol ethers, the use of xanthate radical precursors **2′** allows to suppress the single electron transfer step and favor the hydroalkylation process.[40–45] The hydroalkylation of enamides was examined first. Terminal enamides afforded the desired hydroalkylated products **48–52** in excellent yields (Scheme 9). Reaction involving a non-terminal enamide led to the hydroalkylated products **53** in satisfactory yields. Similar results were obtained with terminal (**54** and **55**) and non-terminal enecarbamates (**56–60**). These results diverges from the one obtained by Gillaizeau *et al.* who have obtained the product of non-reductive alkylation by performing the reaction between xanthates and enamides in the presence of dilauroyl peroxide acting as a radical initiator and oxidant,[46] demonstrating the mildness and non-oxidative character of the triethylborane-involved initiation process.

The efficient hydroalkylation of *N*-alkenyloxazolidinones reported in Scheme 9 offers the possibility of controlling the




Scheme 9 Hydroalkylation of enamides and enecarbamates.




Scheme 10 Stereoselective radical hydroalkylation of chiral enecarbamates. Single crystal X-ray structure of **71** (ellipsoids drawn at 50% probability).

stereoselectivity of the process by using enecarbamates **61** derived from chiral oxazolidinones.[47–51] Reactions involving the terminal 1-substituted *N*-prop-1-en-2-yloxazolidinones provided compounds **62–64** in high yield but poor stereocontrol. Fortunately, reactions involving the non-terminal enecarbamates proceeded with good to high diastereocontrol as illustrated by the formation of compounds **65–71**. These results are in agreement with results obtained for the hydroamination of similar enecarbamates.[48] The highest diastereoselectivity being observed for the 4-isopropyloxazolidin-2-ones leading to **65**, **67**, and **69** with dr ranging from 94 : 6 to 99 : 1. Reactions involving 4-phenyloxazoldin-2-one provided **66**, **68**, **70** and **71** with slightly lower diastereoselectivities varying from 86 : 14 to 92 : 8. The relative configuration of **71** was confirmed by single crystal X-ray crystallography of the major diastereomer (Scheme 10).[33–37] The stereochemical outcome of the process can be rationalized by radical addition from the less hindered face (anti to the 4-phenyl substituent) of the enecarbamate lying in its most stable s-*trans* conformation as proposed by Studer and coworkers for the related hydroamination process.[48,52,53] Interestingly, the diphenyloxazolidinone derivative **70** was easily converted to the corresponding enantiomerically pure protected γ-amino acid (*R*)-**72** under mild hydrogenolysis conditions.[54]

## Conclusions

We have developed a general and operationally simple radical chain process for the hydroalkylation of electron-rich terminal and non-terminal alkenes with α-iodo- and α-xanthylesters. The reaction is initiated with triethylborane and air while the inexpensive and non-toxic TBC is used as a source of hydrogen atom. Highly diastereoselective hydroalkylation was also achieved by using chiral enecarbamates, providing access to chiral γ-amino acid derivatives.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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