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Regiodivergent Addition of Carbon Units to Dual-Activated Alkynes for Stereoselective Construction of Tetrasubstituted Alkenes

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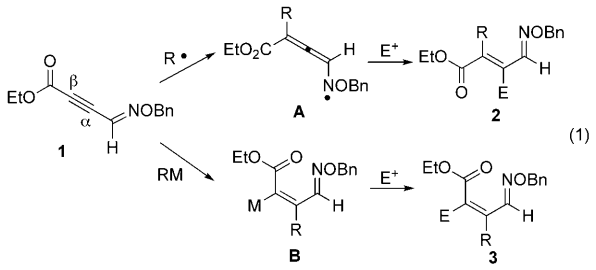
The discovery of potential synthons and reagent systems that allow the selective synthesis of target compounds is crucial for advances to be made in organic synthesis. Development of a simple methodology for preparing both regioisomers from a single substrate with highly tunable selectivity, by designing and controlling of reagents, is an attractive and challenging task. A plethora of stereoselective conjugate addition reactions to α,β-unsaturated carbonyl compounds have been invented.[1] In addition, α,β-unsaturated imines have been reported as a substrate for a number of transformations such as 1,4- and 1,2-addition reaction and cycloaddition reaction.[2] However, switchable regiodivergent addition to an electron-deficient olefins is quite rare. During the course of our studies on radical addition to a variety of α,β-unsaturated imine derivatives,[3] we were interested in the reactivity of alkyne **1** that is doubly activated by an ester and an oxime ether.[4] The alkynyl oxime ether **1** has several reaction sites such as electrophilic carbon atoms and the nitrogen, radicophilic carbon atoms and an acidic hydrogen, therefore, it is one of the most challenging organic compounds [Eq. (1)].



(1)

We anticipated that an alkyl radical would react exclusively at the β-position to generate the allenaminyl radical **A** because it is stabilized by a two-center, three-electron bonding effect.[5] On the other hand, the reaction with a alkynophilic nucleophile such as organocuprate would lead to the generation of α-adduct **B** through addition of an alkyl anion at the more electrophilic α-position. Furthermore, both intermediates could be transformed stereoselectively to a tetrasubstituted alkene by electrophilic trapping under suitable conditions. Herein, we report the reagent-controlled regiodivergent addition reaction of a dual activated alkyne and its application to stereoselective domino and one-pot reactions for the construction of tetrasubstituted alkenes. Owing to their simplicity, convenience, complete positional selectivity, and generally high levels of regiochemical control, both tunable regioselective addition reactions provide a new entry to highly functionalized alkenes.[6] Regiochemically and geometrically defined alkenes are not only ubiquitous structural motifs in biologically relevant molecules, but also serve as a foundation for a broad range of chemical transformations.[7]

In order to test our hypothesis, we started to investigate the reaction of *Z*-alkynyl oxime ether **1**[8] in the presence of a range of alkyl iodides as carbon radical precursors in the iodine-atom-transfer reaction initiated by Et_3B (Table 1). When Z-**1** was treated with cyclohexyl iodide and Et_3B at room temperature, the expected regioselective radical addition reaction proceeded to give β-adduct **4a** in high yield but with low stereoselectivity (Table 1, entry 1). To control the double bond geometry, the radical reaction and the protonation of boryl aminoallene **C**, generated by trapping of allenaminyl radical **A** with Et_3B, were carried out in the presence of alcohol at −80 °C. Addition of *t*BuOH improved the stereoselectivity of the C=N double bond, but not of the C=C double bond (Table 1, entry 2). Interestingly, both double bonds were successfully controlled by the presence

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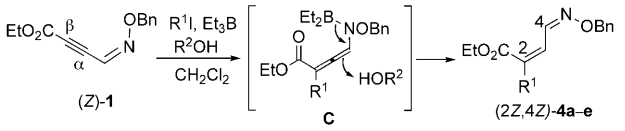
Table 1. Regio- and stereoselective radical addition to alkynyl oxime ether (*Z*)-**1**.[a]



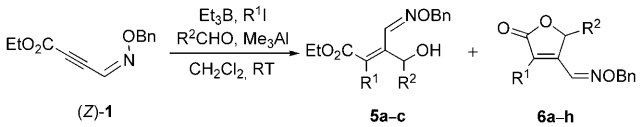
Entry	R^1I	R^2OH	*T* [°C]	Product (yield [%][b])	Ratio[c] [2*Z*,4*E*/2*E*,4*E*/2*Z*,4*Z*/2*E*,4*Z*]
1	*c*-$C_6H_{11}I$	none	RT	**4a** (93)	1:1:2:2
2	*c*-$C_6H_{11}I$	*t*BuOH	−80	**4a** (55)	0:0:3:2
3	*c*-$C_6H_{11}I$	MeOH	−80	**4a** (85)	0:0:10:1
4	*s*BuI	MeOH	−80	**4b** (49)	0:0:15:1
5	*c*-C_5H_9I	MeOH	−80	**4c** (69)	0:0:9:1
6	*i*PrI	MeOH	−80	**4d** (52)	0:0:10:1

[a] The reactions were carried out with R^1I (20 equiv), Et_3B (2 equiv), and R^2OH (2 equiv). [b] Combined yield of all isomers. [c] Determined by ^1H NMR spectroscopy.

of MeOH to furnish (2*Z*,4*Z*)-**4a** in high yield (Table 1, entry 3). Other secondary alkyl iodides worked well to afford the 2*Z*-adducts **4b–d** stereoselectively (Table 1, entries 4–6).

The new finding of this regioselective addition to **1** prompted us to explore a new domino radical addition–aldol-type reaction[9] and we succeeded in developing a novel method for constructing the tetrasubstituted olefins **5** and the highly substituted butenolides **6** (Table 2). In the presence of Me_3Al as a Lewis acid, the domino reaction of **1** with benzaldehyde and Et_3B afforded **5a** and **6a** through a sequential process involving a regioselective ethyl radical addition and a aldol-type reaction of intermediate *N*-boryl aminoallene **C**, but with low selectivity (Table 2, entry 1). In the case of the reaction with aliphatic aldehydes, slightly predominant formation of furanone **6** was observed (Table 2, entries 2 and 3). Interestingly, employment of more bulky secondary isopropyl iodide afforded furanone

Table 2. Domino alkyl radical addition–aldol-type reaction of (*Z*)-**1**.

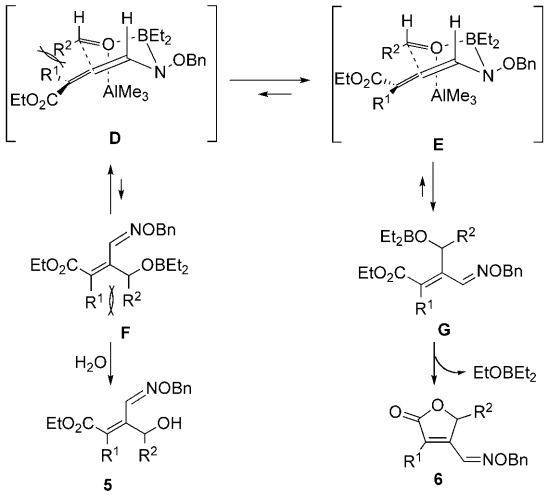


Entry	R^1I	R^2CHO	Product (R^1 =) (yield [%][a]) **5a–c**		**6a–h**	
1[b]	–	PhCHO	**5a** (Et)	(36)	**6a** (Et)	(21)
2[b]	–	Me_2CHCHO	**5b** (Et)	(28)	**6b** (Et)	(55)
3[b]	–	*c*-$C_6H_{11}CHO$	**5c** (Et)	(31)	**6c** (Et)	(49)
4[c]	*i*PrI	PhCHO	nd[d]		**6d**	(77)
5[c]	*t*BuI	PhCHO	nd		**6e**	(93)
6[c]	*i*PrI	*c*-$C_6H_{11}CHO$	nd		**6f**	(63)
7[c]	*c*-$C_6H_{11}I$	*c*-$C_6H_{11}CHO$	nd		**6g**	(68)
8[c]	*t*BuI	*c*-$C_6H_{11}CHO$	nd		**6h**	(68)

[a] Yield of isolated product. [b] Reactions were carried out with Et_3B (2.5 equiv), aldehyde (1.2 equiv), and Me_3Al (1.2 equiv) for 3 h. [c] Reactions were carried out with Et_3B (2.5 equiv), R^1I (20 equiv), aldehyde (1.2 equiv), and Me_3Al (1.2 equiv) for 3 h. [d] Not detected.

6d as a sole product in 77% yield (Table 2, entry 4). It is noteworthy that reversal of stereoselectivity in the aldol reaction step was observed compared with the radical addition–protonation reaction because of thermodynamic control. The reaction with the bulky *tert*-butyl radical also produced exclusively *anti*-adduct **6e** in excellent yield (Table 2, entry 5). The domino reaction with enolizable cyclohexanecarboxaldehyde proceeded effectively to provide the corresponding furanones **6f–h** in good yields and in a stereoselective manner (Table 2, entries 6–8).

The stereoselectivity could be explained with the six-membered transition states **D** and **E** shown in Scheme 1. The tetrasubstituted olefin **5** would be formed through a



Scheme 1. Explanation for the stereoselective outcome of the aldol-type reaction of *N*-boryl aminoallene.

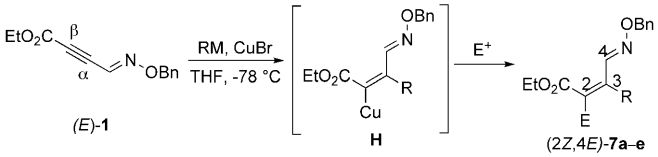
syn-addition of *N*-borylaminoallene **C** to a Me_3Al-activated aldehyde via transition state **D**. An *anti*-trapping of **C** with an aldehyde and subsequent lactonization of borate **G** would afford furanone **6** via transition state **E**. Relatively large alkyl group for R^1 and R^2 would led to a preference for conformation **E** with less steric repulsion between the ester group and the aldehyde part, and eventually led to the formation of furanone **6** through *anti*-addition of an electrophile. Because the aldol reaction in principle is reversible, the irreversible lactonization enforced an equilibrium favoring the formation of furanone **6**.

The usefulness of dual activated alkyne **1** as a synthon was proved by reversed regioselective addition of organocuprates. The conjugate addition of organocopper reagents to the alkynyl ester is a prime method for constructing isomerically pure, trisubstituted α,β-unsaturated esters.[10] Unfortunately, extensions toward synthesizing tetrasubstituted alkenes[11] have been hampered by the low reactivity of the 1-alkoxycarbonyl vinylcopper(I) intermediate and its tendency to isomerize via a copper allenoate at temperatures above −30°C.[12] Although many examples of nucleophilic addition to α,β-acetylenic ketones and esters have been re-

ported,[13] the reaction of α,β-acetylenic imines has not been reported so far.

The regioselective addition reaction of (*E*)-**1**[14] with MeLi in the presence of CuBr·SMe_2 proceeded successfully to give the expected α-addition product (2*Z*,4*E*)-**7a** in moderate yield with high stereoselectivity (Table 3, entry 1). It is noteworthy that the alkylation occurred at the opposite position compared with that of the radical addition, which is consistent with our hypothesis. EtLi worked better than MeLi to afford **7b** in good yield (Table 3, entry 2). The Grignard reagents underwent the same type of α-addition but with no stereoselectivity (Table 3, entry 3). Encouraged by the regioselective nucleophilic α-addition to **1**, we were challenged to explore the one-pot nucleophilic–electrophilic addition reaction and succeeded in constructing tetrasubstituted olefins. Treatment of **1** with R_2CuLi in THF followed by addition of an electrophile such as MeI and PhCOCl, produced the expected tetrasubstituted alkenes **7c** and **7d** with good to high stereoselectivities (Table 3, entries 4 and 5). It should be noted that methylation and bromination by 2,4,4,6-tetrabromo-2,5-cyclohexadienone gave highly functionalized olefin **7e**, which is a useful synthon for further transformation.

Table 3. Regio- and stereoselective nucleophilic addition to alkynyl oxime ether (*E*)-**1**.

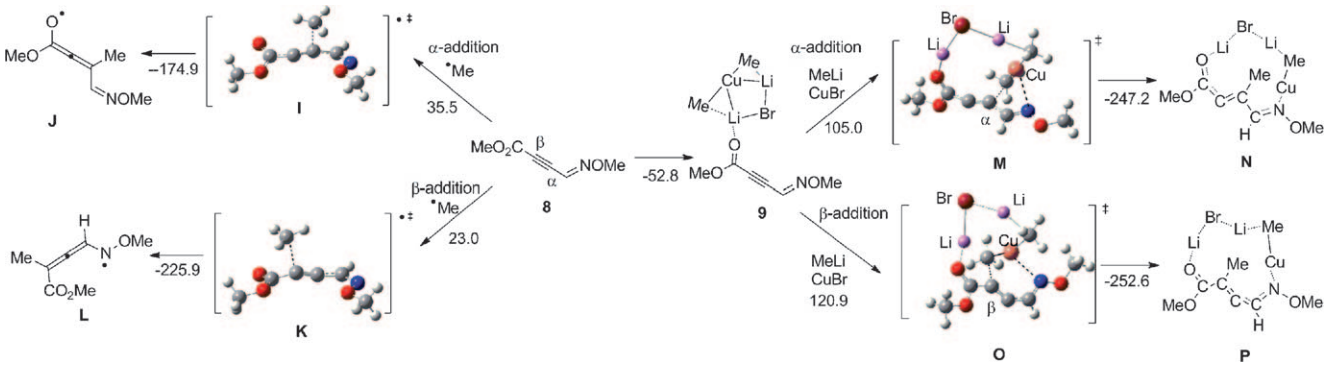


Entry	RM	Electrophile	Product (E=)	Yield [%][a]	Ratio[b] [2*Z*,4*E*/ isomers]
1[c]	MeLi	H_2O	**7a** (H)	46	>10:1
2[c]	EtLi	H_2O	**7b** (H)	75	10:1
3[c]	EtMgBr	H_2O	**7b** (H)	60	1:1
4[d]	EtLi	MeI	**7c** (Me)	63	8:1
5[d]	EtLi	BzCl[e]	**7d** (Bz)	66	>10:1
6[d]	MeLi	TBCHD[f]	**7e** (Br)	45	7:1

[a] Combined yield of the different isomers. [b] Determined by ^1H NMR spectroscopy. [c] Reactions were carried out with RM (2.2 equiv) and CuBr·SMe_2 (1.1 equiv). [d] Reactions were carried out with RM (2.2 equiv), CuBr·SMe_2 (1.1 equiv), and an electrophile (2.2 equiv). [e] Bz: benzoyl. [f] TBCHD: 2,4,4,6-tetrabromo-2,5-cyclohexadienone.

Computational studies were carried out by using density functional theory (DFT) to understand the reversal of regioselectivity with the same substrate (Scheme 2). Addition of a methyl radical to the model oxime ether **8** is predicted to be a highly exothermic process. The activation energy for transition state **K**, which is involved in the addition reaction at the β-carbon of **8**, is calculated to be 23.0 kJ mol^{-1} and, therefore, 12.5 kJ mol^{-1} lower than that for transition state **I**, which is involved in the reaction at the α-carbon. Intermediate **L**, which is involved in the β-addition, is also calculated to be more stable than adduct **J**, which is involved in the α-addition, by 63.5 kJ mol^{-1}. Thus, the β-addition of the methyl radical is both kinetically and thermodynamically preferable to the α-addition. In the case of carbocupration, transition states **M** and **O**, which are involved in the carbocupration of oxime ether **8** with Me_2CuLi, were formed in the presence of LiBr. Inspection of the transition structures reveals that in both structures the lithium atom coordinates with the oxygen of the carbonyl group, and the copper atom coordinates with the nitrogen of the oxime moiety. The carbocupration reaction is predicted to commence from complex **9** in which a lithium atom of the cyclic cluster of Me_2CuLi and LiBr coordinates to the carbonyl group of **8**. The α-addition involving transition state **M** is calculated to be energetically favored over the β-addition involving transition state **O** by 15.9 kJ mol^{-1}. In addition, the α-adduct **N** is calculated to be more stable than the β-adduct **P** by 10.5 kJ mol^{-1}. Therefore, the α-addition is both kinetically and thermodynamically preferable to the β-addition.[15]

In summary, reagent-dependent regioselective additions to dual activated alkynes have been carried out for the first time. The reactions display complete reagent selectivity in that the reversal of the orientation of the addition to the alkynes is controlled. Finally, the present regioselective addition reaction to alkynes can provide a new synthetic access to tetrasubstituted and functionalized alkenes including highly substituted furanones.



Scheme 2. Reaction profile for the regioselective addition reaction of oxime ether **8**. Energies [kJ mol^{-1}] were calculated on the BHandHLYP/6-31+G* level for the radical reactions and on the BHandHLYP/6-31+G*+LanL2DZ ECP level (Cu, Br) for the carbocupration.

Experimental Section

General procedure for radical additions: MeOH (0.011 mL, 0.26 mmol), R^1I (2.6 mmol), and Et_3B (1.0 M in hexane, 0.26 mL, 0.26 mmol) were added to a solution of alkynyl oxime ether (*Z*)-**1** (30 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) under a N_2 atmosphere at −80 °C. After being stirred for 15 h at the same temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (3×20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexane/AcOEt 15:1) afforded **4a–d**.

General procedure for domino alkyl radical addition–aldol-type reactions: R^2CHO (0.26 mmol), R^1I (4.40 mmol), Me_3Al (1.03 M in hexane, 0.25 mL, 0.26 mmol), and Et_3B (1.05 M in hexane, 0.52 mL, 0.55 mmol) were added to a solution of (*Z*)-**1** (50 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) under an Ar atmosphere at room temperature. After being stirred under a N_2 atmosphere at the same temperature for 3 h, the reaction mixture was washed with saturated aqueous $NaHSO_3$ (10 mL) and extracted with ethyl acetate (3×20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL), dried over $MgSO_4$, and concentrated at reduced pressure. The residue was purified by preparative TLC (hexane/AcOEt 5:1) to afford **6d–h**.

General procedure for nucleophilic and electrophilic addition reactions: RLi (0.48 mmol) was added dropwise to a suspension of CuBr·Me_2S (50 mg, 0.24 mmol) in THF (1 mL) under an Ar atmosphere at −40 °C. The resulting dark brown suspension was stirred at the same temperature for 1 h. A solution of (*E*)-**1** (50 mg, 0.22 mmol) in THF (1 mL) was added dropwise to the reaction mixture at −78 °C and then the reaction mixture was stirred at the same temperature for 1 h. After a solution of an electrophile (0.48 mmol) was added dropwise, the reaction mixture was stirred at −78 °C for 1 h, and then 0 °C for 1 h. After being stirred at room temperature overnight, the reaction was quenched with saturated aqueous NH_4Cl (5 mL), diluted with H_2O (10 mL), and extracted with ethyl acetate (3×20 mL). The organic phase was washed with saturated aqueous NaCl (20 mL), dried over $MgSO_4$, and concentrated at reduced pressure. The residue was purified by preparative TLC (hexane/AcOEt = 10:1) to afford **7c–e**.

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Keywords: addition reactions · computational chemistry · domino reactions · radical reactions · regioselectivity

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[8] The geometry of the starting oxime ether is not a concern. Indeed, the cyclohexyl radical addition to (*E*)-**1** afforded **4a** with the same stereoselectivity.

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[14] The *E* isomer of the oxime ether should be used, because the reaction of (*Z*)-**1** with organometallic reagent produced the conjugated nitrile by the elimination of benzyl alcohol.

[15] For details of calculations see the Supporting Information.

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