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Formation of β-Oxo-*N*-vinylimidates via Intermolecular Ester Incorporation in Huisgen Cyclization/Carbene Cascade Reactions

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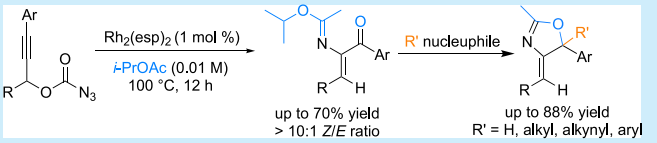
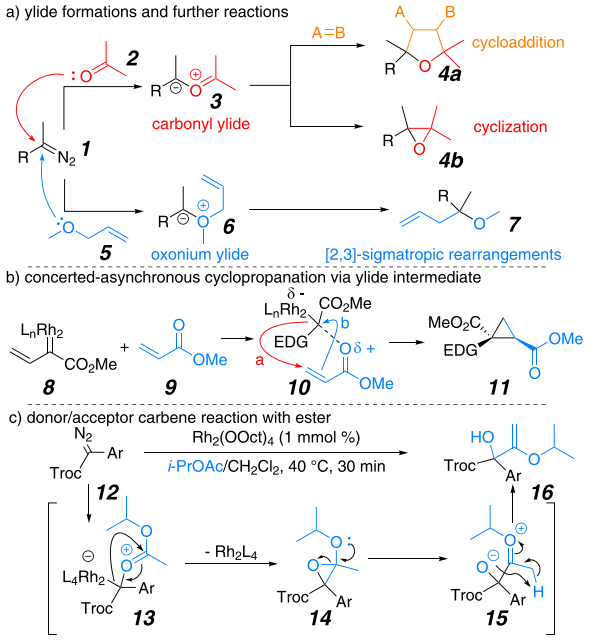
ABSTRACT: Unusual intermolecular trapping of esters by carbenes generated via a Huisgen cyclization/retroelectrocyclization/dediazotization cascade reaction is presented. β-Oxo-*N*-vinylimidates could be obtained in one step from propargyl carbonazidates. Mechanistic control experiments suggested reversible dipole formation by ester addition to the carbene, and nitrogen attack to the ester carbonyl was irreversibly followed by stereoselective decarboxylative elimination to give the *Z*-vinyl imidate. The cross-conjugated enone, imidate, and enamine functional groups in the β-oxo-*N*-vinylimidates offer novel syntheses of functionalized oxazoles.

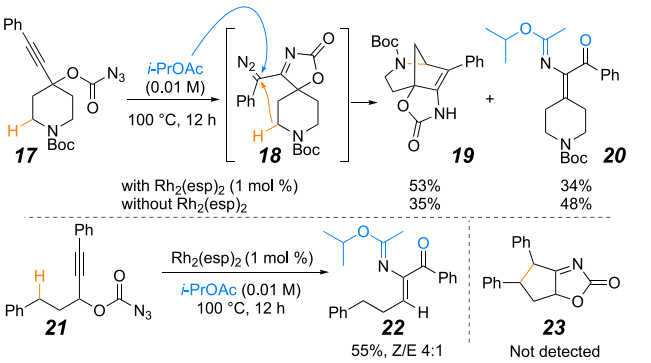


The considerable reactivity of carbenes[1] promotes many useful synthetic transformations: C−H insertion,[2] X−H insertion,[3−5] cyclopropanation,[6] ylide formation,[7] and cycloaddition.[8] Electrophilic carbenes, often derived from diazo compounds like **1** (Scheme 1a), engage in ylide formation with oxygen-containing Lewis bases such as ketones (e.g., **2**) and ethers (e.g., **5**) to form carbonyl ylides **3**[7b,c,8] and oxonium ylides **6**,[7d−g] respectively. Highly reactive carbonyl ylides **3** can undergo cycloaddition or cyclization to build oxacycles **4a**[7b,c] or epoxides **4b**.[7c,d,9] Allyl-substituted oxonium ylides **6** can undergo [2,3]-sigmatropic rearrangements to form homoallyl ethers **7**.[7e,f] Carbonyl ylide formation can be intermolecular or intramolecular. Intermolecular reactions between carbenes and ketones or aldehydes are well developed.[7a−d,10] However, intermolecular reactions between carbenes and esters are rare,[9] despite many examples of intramolecular ester ylide formation.[7a−d,11] In fact, methyl benzoate was a stabilizing additive in rhodium-catalyzed cyclopropanation.[12] A similar stabilizing interaction was seen in the cyclopropanation of carbene **8** (Scheme 1b).[13] The *in situ* formation of ylide **10** not only facilitated the nucleophilic attack by the Rh−C bond on the acrylate **9** (arrow a) but also prevented the self-

Scheme 1. Ylide Formation in Carbene Chemistry



Scheme 2. Huisgen Cyclization/Carbene *i*-PrOAc Cascades



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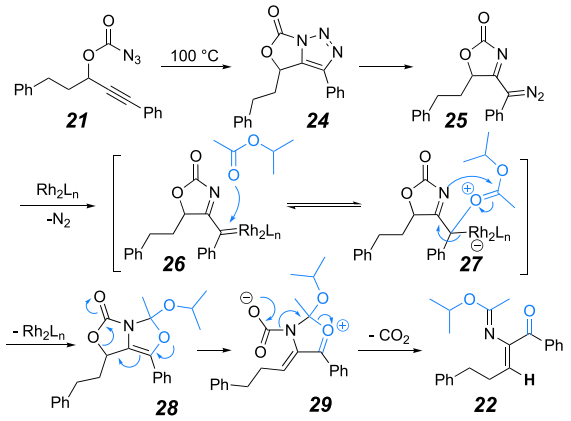
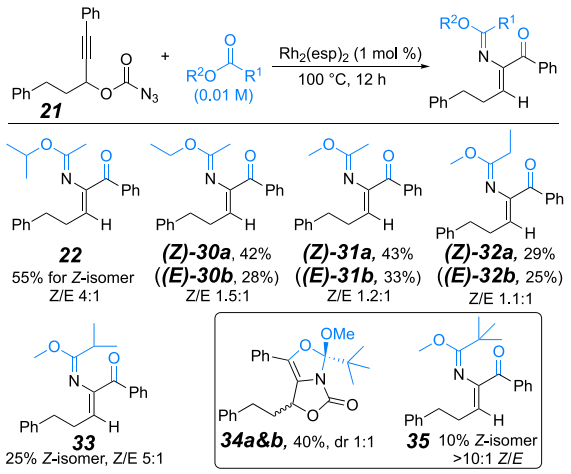
Scheme 3. Proposed Mechanism[a]



[a]In those reactions without rhodium, a free carbene is assumed.

Scheme 4. Ester Scope[a]



[a]Isolated yields; Z/E ratio determined by ^{1}H NMR analysis of peak integration of crude material.

decomposition of carbene **8**. Thus, esters have been efficiently used as solvents in various rhodium-catalyzed carbene reactions.[14,15] To the best of our knowledge, the only intermolecular carbene reaction with esters was reported in 2018 by Davies,[9] where donor/acceptor carbenes **12** reacted with esters to form tertiary alcohols **16** (Scheme 1c).

In a recent paper, we reported a Huisgen cyclization/carbene cascade reaction to construct bridged azacycles and propellanes.[15] Investigations showed that the best solvent for that transformation was isopropyl acetate (*i*-PrOAc). However, an unexpected imidate **20** was found as a byproduct in 34% yield (Scheme 2). Interestingly, the imidate **20** became the favored product without $Rh_2(esp)_2$ (48% yield). Furthermore, in the cascade reaction with acyclic carbonazidate **21**, only imidate **22** was isolated (55% yield), and no fused bicyclic product **23** was detected. These results were inspiring, since the reaction not only juxtaposes cross-conjugated enone, imidate, and enamine functional groups in the product after a single step, but it must also proceed through an unusual mechanism. Moreover, Z/E-diastereoselectivity was observed in this reaction, with only the *Z*-isomer of imidate **22** isolated.

The discovery of novel enone-linked imidates like **20** and **22** prompted further investigation. To avoid competing C−H insertion reactions, acyclic carbonazidate **21** was used for the optimization, and the best conditions turned out to be the same as those in our previous cascade reaction.[15,16] The reaction also occurred without rhodium catalysis, but in a lower yield. In contrast, the cyclic substrate **17** gave a higher yield of imidate **20** without $Rh_2(esp)_2$ (48%) than for the catalyzed reaction (34%). This suggests that if there is competing C−H insertion, more imidate may be formed without rhodium catalysis. Different dirhodium and other metal catalysts were examined, but the yield did not improve.[16] Gratifyingly, a 47% yield was obtained at a 1 mmol scale with a concentration of 0.02 M. We also tested comparable conditions to Davies' for intermolecular carbene-ester reactions[9] and other mixed solvent systems; however, the yield was significantly lower.[16]

A proposed mechanism is shown (Scheme 3). Carbonazidate **21** would first undergo Huisgen cyclization to form triazole **24** as was the case in our previous studies.[15,17] After the subsequent triazole ring opening in the presence of a dirhodium catalyst, α-diazoimine **25** and then rhodium α-iminocarbene **26** would be generated. Although the precise role of the rhodium catalyst is still unclear, we believe it stabilizes the carbene intermediate to avoid detrimental reactivity. Then, nucleophilic addition to rhodium carbene **26** by the carbonyl oxygen of *i*-PrOAc would occur to form carbonyl ylide **27**. We hypothesize that the formation of ylide **27** from rhodium carbene **26** and *i*-PrOAc is reversible, and the highly reactive ylide **27**, formed *in situ*, would generate oxazole **28** by cyclization. The alkoxy oxazole **28** would be unstable and could undergo elimination and decarboxylation to generate imidate **22**. During the new C=C π bond formation from **28** to **29**, the transient 1,3-allylic strain of the phenyl and alkyl substituents would favor formation of *Z*-isomer **29**.

The scope of esters was then explored (Scheme 4). From carbonazidate **21** with *i*-PrOAc, the *Z*-isomer of **22** was isolated in 55% yield. The minor *E*-isomer was less stable than the *Z*-isomer and was not isolable; it was only observed in the crude NMR with a 4:1 Z/E ratio of isomers. With EtOAc, a good combined yield of **30a** and **30b** (70%) was observed, and each isomer could be isolated; however, the reduced steric interactions also impacted the Z/E ratio and the selectivity between **30a**:**30b** was only 1.5:1. Further reducing the size of the ester by using MeOAc gave imidates **31a** and **31b** as a 1.3:1 Z/E-isomer mixture after purification with a 76% combined yield. Methyl propionate was also used to produce imidates **32a** and **32b** with a 54% combined yield. In comparison to EtOAc, the size of alkyl group connected to the carbonyl has a greater impact than the size of the alkoxyl on the yield (reduced to 54% from 70% for EtOAc), but the configuration outcomes (Z/E ratio, 1.2:1 to 1.5:1) were similar. Interestingly, the configuration of the imidate π bond did not change, which indicates that the structure of the ester does not impact the geometry of the imidate after decarboxylation (from **29** to **22**, Scheme 3). Methyl isobutyrate gave **33** with a 5:1 Z/E ratio before purification and a 25% isolated yield for the pure *Z*-isomer. Bulkier esters like methyl pivalate gave product **34**, which did not decarboxylate, in 40% yield with 1:1 dr. Only a small amount of the imidate **35** formed.

A carbonazidate with an isobutyl group (**36**, Table 1) can react with esters as well, and a single isomer of imidate **37** was isolated in 33% yield with *i*-PrOAc (entry 1). Bicyclic product **38**, formed by C−H insertion, was also isolated in 39% yield. As was seen above, EtOAc caused an increase in the combined

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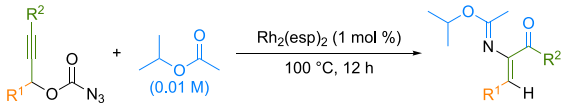
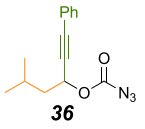
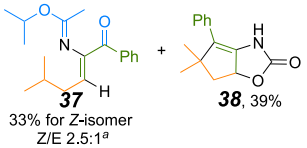
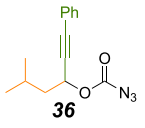
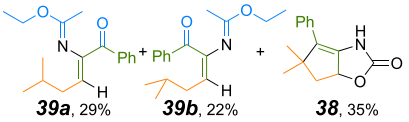
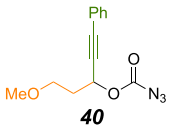
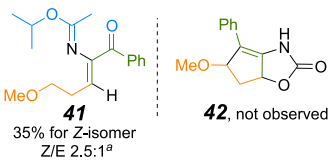
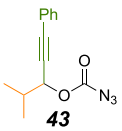
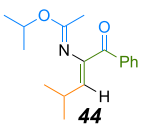
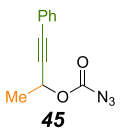
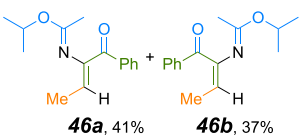
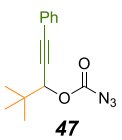
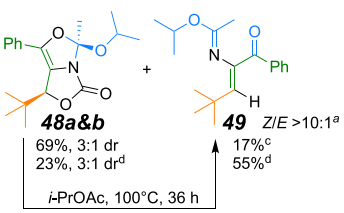
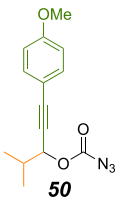
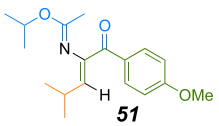
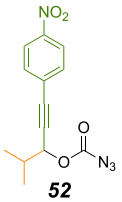
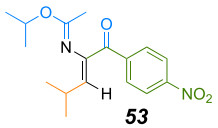
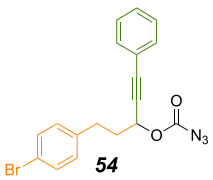
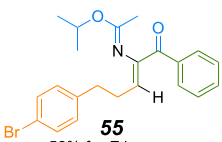
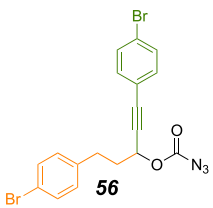
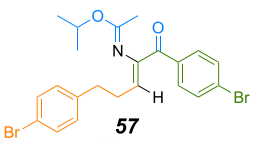
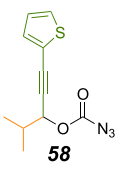
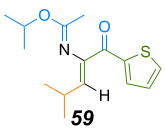
Table 1. Carbonazidate Scope[a]



entry	carbonazidate	product(s)[a]
1	 **36**	 **37** 33% for *Z*-isomer *Z*/*E* 2.5:1[a] **38**, 39%
2[b]	 **36**	 **39a**, 29% **39b**, 22% *Z*/*E* 1.3:1[a] **38**, 35%
3	 **40**	 **41** 35% for *Z*-isomer *Z*/*E* 2.5:1[a] **42**, not observed
4	 **43**	 **44** 67% for *Z*-isomer *Z*/*E* > 10:1[a]
5	 **45**	 **46a**, 41% **46b**, 37% *Z*/*E* 1.1:1[a]
6	 **47**	 **48a&b** 69%, 3:1 dr 23%, 3:1 dr[d] **49** *Z*/*E* >10:1[a] 17%[c] 55%[d] *i*-PrOAc, 100°C, 36 h

entry	carbonazidate	product(s)[a]
7	 **50**	 **51** 59% for *Z*-isomer *Z*/*E* 4:1[a]
8	 **52**	 **53** 64% for *Z*-isomer *Z*/*E* > 10:1[a]
9	 **54**	 **55** 52% for *Z*-isomer *Z*/*E* 3:1[a]
10	 **56**	 **57** 59% for *Z*-isomer *Z*/*E* > 10:1[a]
11	 **58**	 **59** 69% for *Z*-isomer *Z*/*E* > 10:1[a]

[a]Isolated yields; *Z*/*E* ratio determined by ^{1}H NMR analysis of peak integration in crude material. [b]EtOAc was used instead of *i*-PrOAc. [c]Yield determined by NMR. [d]Reaction time 36 h.

yield of imidates **39a** and **39b** along with a decrease in configurational selectivity (entry 2). Meanwhile, 35% of bicyclic product **38** was also isolated. Surprisingly, carbonazidate **40** did not produce any observable bicyclic C−H insertion product **42**. In this case, only the *Z*-isomer of imidate **41** was isolated in 35% yield (entry 3). This result is unusual because C−H bond insertion next to ether oxygens is usually regarded as being more facile.[2a] To avoid C−H insertion on the isobutyl side chain, an isopropyl substituted carbonazidate, **43**, was used. Imidate **44** was produced in 67% yield for the *Z*-isomer with a *Z*/*E* ratio greater than 10:1 (entry 4). Another reason for the increase of yield could be due to the Thorpe−Ingold effect, with a larger substituent (isopropyl vs methylene) facilitating Huisgen cyclization (i.e., **21** to **24**, Scheme 3). Methyl substituted carbonazidate **45** gave a higher combined yield of *Z* and *E* imidates **46a** and **b** (78%, entry 5) than isopropyl carbonazidate **43**. However, a lack of *Z*/*E* selectivity (1.1:1) was observed indicating that stereoselectivity is dependent on substituent size. Carbonazidate **47** produced the carbamate-containing product **48a** and **b** in 69% combined yield with 3:1 dr along with a minor formation of imidate **49** with a *Z*/*E* ratio greater than 10:1 (entry 6), further supporting that the substituent on the secondary carbon in the carbonazidate plays an important role for the olefin stereoselectivity of the product. Extended heating increased the yield of imidate **49**, and the latter's formation directly from purified **48a** and **b** demonstrates that the bicyclic oxazoles are initially formed and decarboxylation leads to the imidates, albeit slowly for *tert*-butyl substitution. Both electron-donating and -withdrawing groups on the phenyl ring caused a decrease of yield (59%, entry 7, and 64%, entry 8). An electron-withdrawing group on the alkynyl phenyl ring (−NO_2, **52**) did not impact *Z*/*E* selectivity; however, with an electron-donating group (−OMe, **50**), a decrease of *Z*/*E* selectivity was observed.

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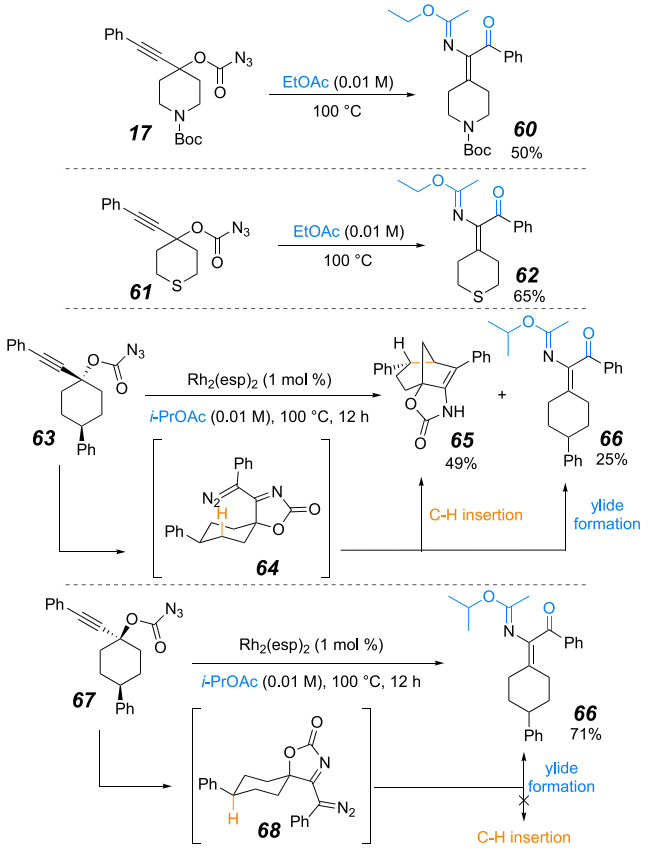
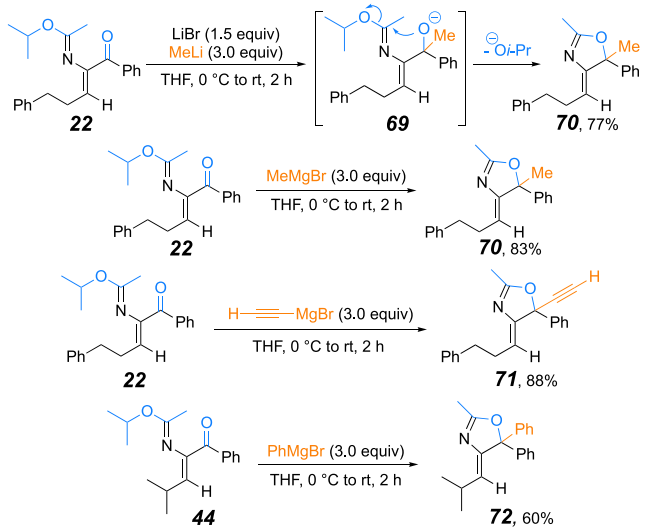
Scheme 5. Cyclic Substrate Scope



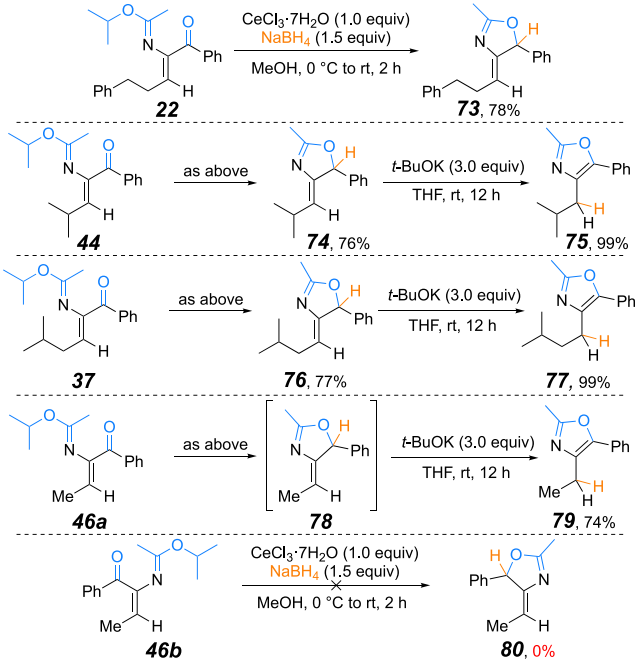
Scheme 6. *exo*-Oxazole Formation via C−C Bond Formation



Brominated carbonazidates **54** and **56** were also utilized for imidate formation, and they gave **55** and **57** in moderate yields, respectively (entries 9 and 10). Furthermore, 4-bromophenylalkynyl carbonazidate **56** increased the *Z*/*E* selectivity to greater than 10:1, which could be due to the ring's more electron-deficient nature. Carbonazidate **58** can yield thiophene-containing[18] imidate **59** in 69% yield (*Z*-isomer) with high *Z*/*E* selectivity (entry 11).

Cyclic carbonazidates were also used for the formation of imidates. To avoid C−H insertion by the carbene intermediate, the rhodium catalyst was excluded. *O*-Ethyl imidate **60** was obtained in 50% yield from heterocycle **17** in EtOAc (Scheme 5). From tetrahydrothiopyran carbonazidate **61**, the imidate **62** was obtained in 65% yield. As the ring conformation of the carbonazidate substrates could impact the outcome of the cascade, substituted rings were investigated. With the carbonazidate tether trans to a phenyl group at the cyclohexyl 4-position (**63**), bridged azacycle **65** was formed in 49% yield along with 25% of imidate **66**. However, when the same conditions were used with cis substrate **67**, imidate **66** was isolated in 71% yield. A possible rationale for this divergent outcome is that intermediate **64**, generated from *trans*-carbonazidate **63**, favored C−H insertion to form bridged azacycle **65** because the equatorial phenyl places the carbene carbon in an advantageous axial position for transannular C−H bond insertion. On the other hand, intermediate **68**, generated from *cis*-carbonazidate **67**, disfavored C−H insertion by placing the carbene in an equatorial position, favoring solvent addition.

Scheme 7. *exo*- and *endo*-Oxazole Formation via Reduction



The novel arrangement of multiple active functional groups, π systems, and heteroatoms in the cascade products is inspiring. To show one example of the combined reactivity, a new synthetic pathway to heterocycles was demonstrated. Oxazoles are present in many natural products and pharmaceuticals due to their Lewis basicity and hydrogen bonding abilities.[19] The enone motif in **22** could undergo 1,2-nucleophilic addition with methyllithium to form tertiary alkoxide **69**, followed by eliminative cyclization to generate the alkylidene oxazole **70** (Scheme 6). Grignard reagents functioned just as well with oxazole formation, providing alkyl-, alkynyl-, and aryl-substituted oxazoles **70**, **71**, and **72** in good to excellent yields.

Alternatively, Luche reduction of imidate **22** gave the unusual *exo*-unsaturated nonaromatic oxazole **73** in 78% yield (Scheme 7). Similarly, imidates **44** and **37** could also undergo reduction to generate *exo*-unsaturated oxazoles **74** and **76** in 76% and 77% yield, respectively. *exo*-Unsaturated oxazoles **74** and **76** could tautomerize to *endo*-oxazoles **75** and **77** with *t*-

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BuOK in quantitative yields. Both *Z*- and *E*- imidates **46a** and **46b** were subjected to reduction. Only the *Z*-imidate **46a** was effective, and tautomerization formed *endo*-oxazole **79** in 74% yield with >95% purity for the two steps without any chromatographic purification after either step.

In conclusion, a Huisgen cyclization/carbene cascade reaction with intermolecular trapping of the in situ carbene intermediate by esters proved to be quite robust. *Z*-Isomer selectivity was demonstrated in many transformations. A proposed mechanism hypothesizes that decarboxylation was the key driving force in the reaction and provided the stereoselectivity. The major competing reactivity was C−H bond insertion, which could be avoided by exclusion of the Rh(II) catalyst. The novel reaction provided imidate products with cross-conjugated imidate, enamine, and ketone motifs that were used successfully in heterocycle synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03619.

Experimental procedures, compound characterization, optimization tables, and copies of spectra (PDF)

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Notes

The authors declare no competing financial interest.

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