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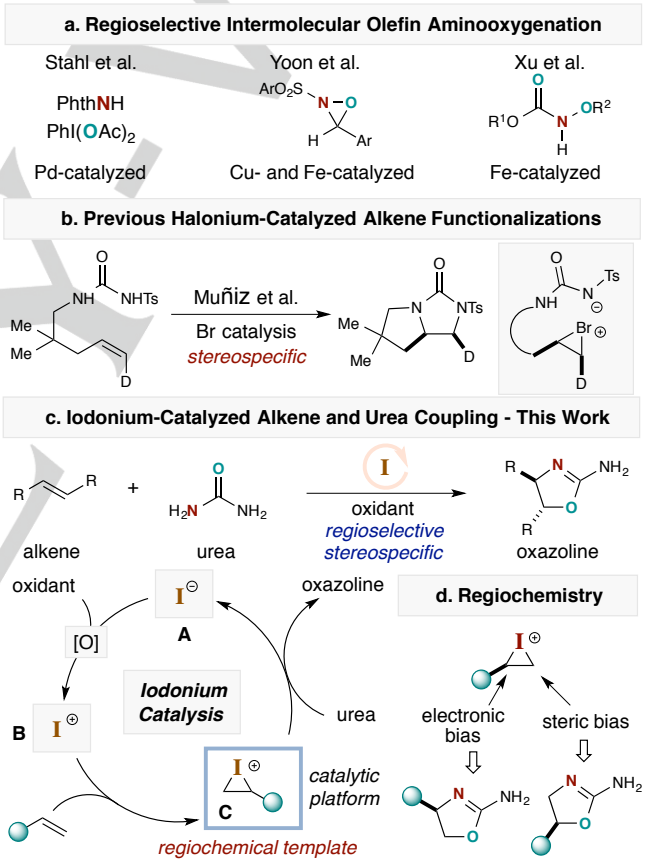
Regioselective Formal [3+2] Cycloadditions of Ureas with Activated and Unactivated Olefins for Intermolecular Olefin Aminooxygenation

Fan Wu, Nur-E Alom, Jeewani P. Ariyarathna, Johannes Naß, and Wei Li*[a]

Abstract: A new class of intermolecular olefin aminooxygenation reaction is described. This reaction utilizes the classic halonium intermediate, as a regio- and stereochemical template, to accomplish the selective oxyamination of both activated and unactivated alkenes. Notably, urea chemical feedstock can be directly introduced as the N- and O-source and simple iodide salt can be utilized as the catalyst. This formal [3+2] cycloaddition process provides a highly modular entry to a range of useful heterocyclic products with excellent selectivities and functional group tolerance.

Regio- and stereoselective aminooxygenation of olefins is an important transformation to generate vicinal amino alcohol derivatives, common motifs in pharmaceuticals, natural products, agrochemicals, and ligand frameworks.[1] The osmium-catalyzed Sharpless aminohydroxylation remains to be the benchmark for this class of reaction.[2] Extensive efforts have been devoted to address the inherent limitations of this pioneering protocol utilizing *intramolecular* substrates, where regioselectivity is often not a concern.[3] Catalytic intermolecular olefin oxyamination, in a regio- and stereoselective manner, however, remains a formidable challenge with limited successful examples.[4] Among them, Yoon reported both Cu- and Fe-catalyzed aminooxygenation of olefins with sulfonyl oxaziridines;[4a-e] Stahl disclosed the Pd-catalyzed aminoacetoxylation of allylic and homoallylic ethers and esters;[4f] Xu developed Fe-catalyzed aminooxygenation of olefins through N–O bond cleavage of hydroxylamines (Scheme 1a).[4g] Despite these excellent advances, the use of unadorned feedstock chemical as the oxyamination reagent, with excellent regioselectivity in intermolecular settings for both activated and unactivated olefins, is exceptionally challenging but greatly desirable. Furthermore, high stereospecificity can be difficult to achieve involving radical or carbocation intermediates.

Our group is interested in the utilization of classic intermediates such as the haloniums, first described by Roberts and Kimball in 1937, as key catalytic intermediates for the regioselective alkene difunctionalizations (scheme 1b).[5] Structural characterizations by Olah,[6] Wyndberg,[7] Brown,[8] Kochi,[9] and Nugent[10] followed by the elegant alkene-to-alkene halonium transfer studies by Brown[8] and Denmark[11], among other important works,[12] have set a solid foundation for halonium as a valuable reactive intermediate in organic synthesis. The catalytic utilization of halonium in alkene functionalizations have recently been investigated by Muñiz for intramolecular diamination reaction and Zhdankin in alkene cyclopropanation and aziridination reactions (Scheme 1b).[13] Notably, excellent stereospecificities can be obtained in these reactions via the putative halonium intermediates.



Scheme 1. Background on Halonium-Catalyzed Regioselective Intermolecular Olefin Oxyamination.

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We envision an iodide catalyst **A** can be oxidized to an iodenium ion **B**, which in turn can couple with an alkene to generate the iodonium **C** (Scheme 1c). A subsequent formal [3+2] cyclization with urea will regenerate the iodide catalyst and afford a valuable N- and O-based heterocycles.[14] More importantly, we reason that an unsymmetric iodonium will present both an electronically biased site and a sterically biased site (Scheme 1d). A selective initial nucleophilic addition to one of these sites constitutes the regiochemcial determining step, will then afford us an opportunity to achieve a highly

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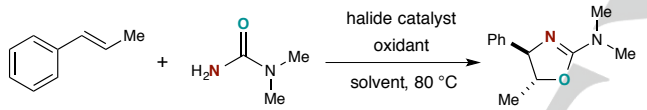
regioselective intermolecular olefin oxyamination process. In addition, we postulate that the involvement of the key iodonium intermediate will render stereospecific processes viable. Our earlier works have demonstrated the capacity of onium-related intermediates in a number of alkene difunctionalizations.[15] Herein, we report our finding of a catalytic *intermolecular* coupling of alkenes and ureas, with iodonium as a regio- and stereochemical template, for the aminooxygenation of both activated and unactivated olefins.

Inspired by the recent examples of hypervalent iodine catalysis,[16] we commenced our studies with *trans*-β-methylstyrene **1** and 1,1-dimethylurea **2** as our standard substrates. Screening a number of oxidants with lithium iodide (LiI) as the catalyst gratifyingly revealed that fluoride-based oxidants, such as Selectfluor and *N*-fluorobenzenesulfonimide (NFSI), were viable oxidants (Table 1, entry 1-3). Interestingly, the reactivity we observed here is distinct from the pioneering fluoro-functionalization works by the Toste group using Selectfluor.[17] In this case, we observed 72% yield of the desired product with Selectfluor and LiI as the oxidant and catalyst combination. Optimization with stoichiometry, iodide catalysts, and temperature revealed LiI being the optimal catalyst and entry 4 being the optimal conditions (Table 1, entry 4-11). Finally, control reactions demonstrated the necessity of both the halide catalyst and the oxidant (Table 1, entry 12 and 13).

Table 1. Optimization Studies for Alkene Urea Coupling.[a]



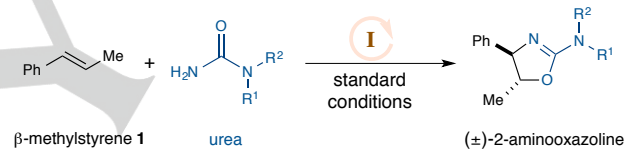
β-methylstyrene **1** 1,1-dimethylurea **2** (±)-2-aminooxazoline **3**

entry	catalyst	oxidant (mol %)	yield (%)[b]	rr	dr
1	LiI	Selectfluor (150)	72	> 95:5	> 95:5
2	LiI	H_2O_2 50% aq (150)	-	-	-
3	LiI	NFSI (150)	33	> 95:5	> 95:5
4	LiI	Selectfluor (120)	75 (69)	> 95:5	> 95:5
5	LiI	Selectfluor (100)	72	> 95:5	> 95:5
6	NaI	Selectfluor (120)	72	> 95:5	> 95:5
7	KI	Selectfluor (120)	22	> 95:5	> 95:5
8	TBAI	Selectfluor (120)	52	> 95:5	> 95:5
9	NH_4I	Selectfluor (120)	55	> 95:5	> 95:5
10[c]	LiI	Selectfluor (120)	61	> 95:5	> 95:5
11[d]	LiI	Selectfluor (120)	61	> 95:5	> 95:5
12	-	Selectfluor (120)	< 5	-	-
13	LiI	-	NR	-	-

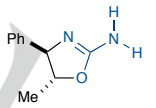
[a] Standard conditions: **1** (0.5 mmol), **2** (1.5 mmol), iodide catalyst (10 mol %), oxidant (0.6 mmol), DCE (0.5 M), 80 ºC, 16 h. Yields were determined by ^{1}H NMR analysis using 1,3-benzodioxole as an internal standard. [b] Yield in parenthesis was isolated yield. [c] **2** (1.0 mmol). [d] 60 °C.

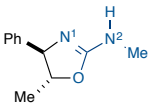
With the optimized conditions in hand, we evaluated the urea substrate scope. A series of urea underwent the coupling process smoothly using the standard reaction conditions. Notably, plain urea, a chemical feedstock produced in million metric tons scale and of special importance in organic synthesis, proceeded effectively to afford the desired product in 35% yield, albeit with slight diminished regioselectivity (Table 2, product **4**). For mono-substituted urea, the increase of steric bulk on one nitrogen of the urea leads to higher chemoselectivity on the un-substituted nitrogen atom (Table 2, product **5**-**8**). The utilization of a chiral auxiliary is, however, ineffective in inducing an asymmetric oxyamination process (Table 2, product **9**). On the other hand, 1,1-disubstituted acyclic urea substrates uniformly produced the desired oxazolines in good yields and excellent regio- and diastereoselectivity (Table 2, products **10** and **11**). In certain cases, we have found that the addition of BF_3•Et_2O as a Lewis acid can improve the reaction yield, similar to what Göttlich observed in analogous copper-catalyzed olefin oxyamination.[18] Urea substrates bearing heterocycles, such as pyrrolidine, piperidine, azepane, morpholine, piperazine, and 1,2,3,4-tetrahydroisoquinoline, all afforded the desired coupling products with exceptional regio- and stereoselectivity (Table 2, products **12**-**17**). Interestingly, both acyclic and cyclic 1,3-disubstituted-ureas could also afford the desired oxazolidine products (Table 2, product **18** and **19**).[19]

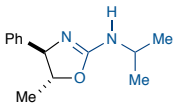
Table 2. Representative Urea Substrate Scope.[a]

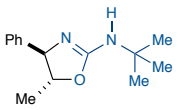


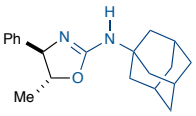
β-methylstyrene **1** urea (±)-2-aminooxazoline

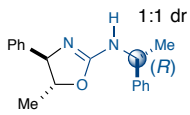

(±)-**4**, 35%, 90:10 rr 95:5 dr


(±)-**5**, 45%, >95:5 rr, >95:5 dr, 81:19 (N^1:N^2)

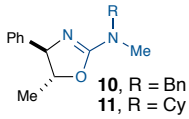

(±)-**6**, 74%, 90:10 rr >95:5 dr

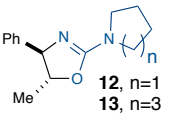

(±)-**7**, 71%, >95:5 rr, dr

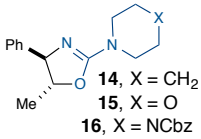

(±)-**8**, 73%, >95:5 rr, dr[b]



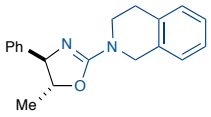
(±)-**9**, 65%, >95:5 rr, dr

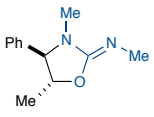

10, R = Bn
11, R = Cy

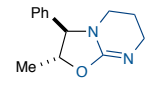

12, n=1
13, n=3


14, X = CH_2
15, X = O
16, X = NCbz

(±)-**10**, 90%, >95:5 rr, dr[b] (±)-**12**, 83%, >95:5 rr, dr[b] (±)-**14**, 73%, >95:5 rr, dr[b]
(±)-**11**, 60%, >95:5 rr, dr (±)-**13**, 70%, >95:5 rr, dr (±)-**15**, 84%, >95:5 rr, dr[b]
(±)-**16**, 87%, >95:5 rr, dr[b]


(±)-**17**, 62%, >95:5 rr, dr[b]

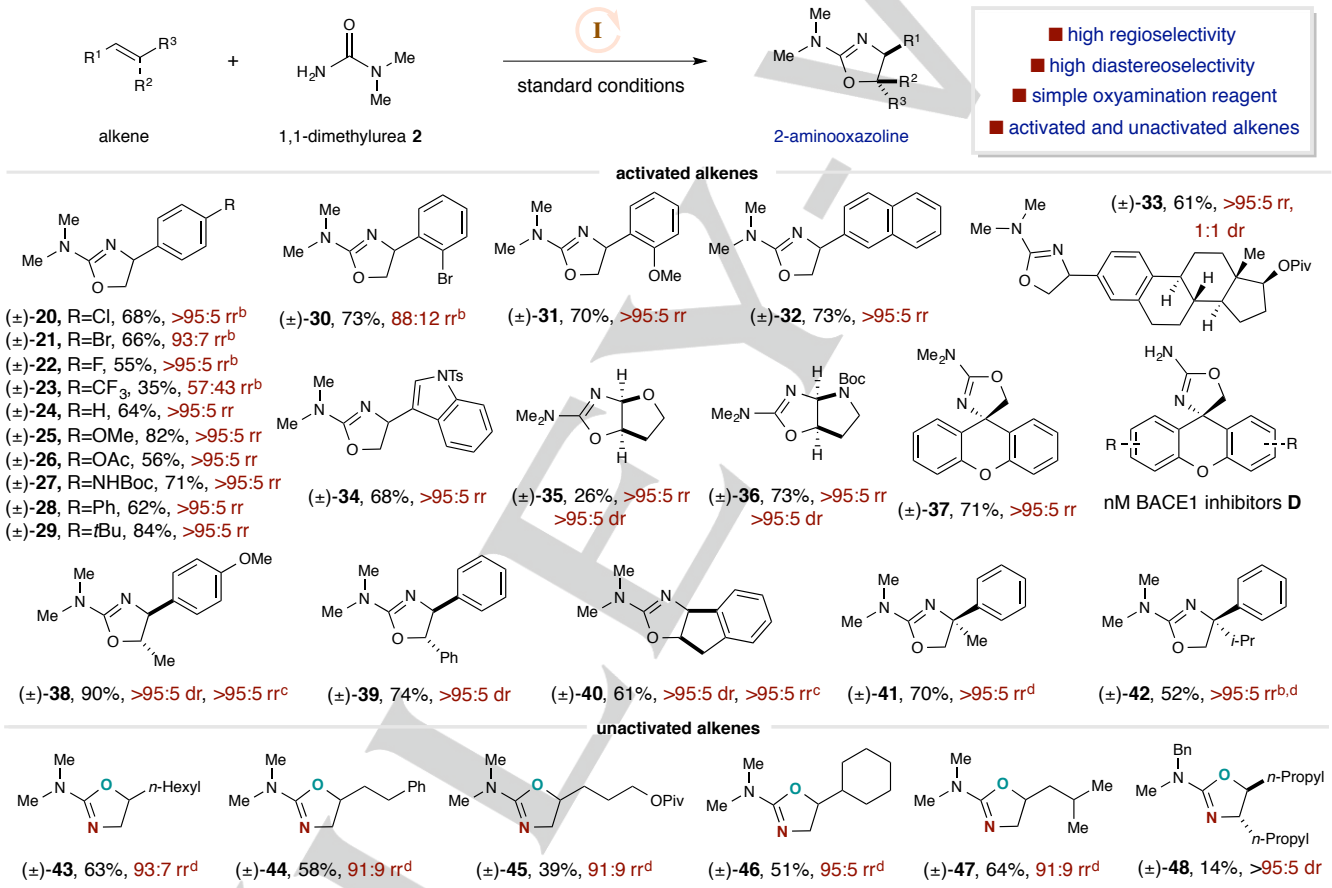

(±)-**18**, 75%, >95:5 rr, dr[b]


(±)-**19**, 72%, >95:5 rr, dr[b]

[a] Standard conditions. Product ratios were determined for crude mixtures based on ^{1}H NMR. Isolated yields were for the major isomer. [b] 1.0 equiv. of BF_3•Et_2O was added.

Delighted by the urea scope, we then turned our attention to the alkene substrate scope. We initially tested a range of mono-substituted styrenyl derivatives. A variety of functional groups including halogens, trifluoromethyl, alkyl, naphthyl, ether, ester, and amine were tolerated in this reaction with high yields and regioselectivity (Table 3, products **20**-**32**).[20] An estradiol-derived alkene proceeded smoothly to a single regioisomeric product (Table 3, products **33**). Electron-rich heterocyclic olefins such as vinylindole, dihydrofuran, and dihydropyrrole were viable substrates to provide the products with excellent regioselectivity (Table 3, products **34**-**36**).[21] Xanthene underwent the desired coupling to provide the spirocyclic aminooxazoline-xanthene **37**, rendering this strategy amenable for analog synthesis of BACE1 inhibitors **D**, which showed robust Aβ reduction in a rat pharmacodynamic model.[22] Moreover, 1,2-disubstituted *trans*- and *cis*-styrenyl derivatives afforded the desired heterocycles in high yields, regio- and diastereoselectivity (Table 3, products **38**-**40**). Notably, 1,1-disubstituted styrenes could effectively produce oxazolines with highly congested carbon stereogenic centers in excellent regioselectivity (Table 3, products **41** and **42**). Importantly, unactivated alkenes such as mono-substituted aliphatic olefins also resulted in the desired heterocycles with good yields and regioselectivity (Table 3, products **43**-**47**). 1,1-disubsituted olefins such as 2-methyl-hexene, however, were ineffective substrates in this reaction, resulted in <5% yield. The 1,2-disubstituted *trans*-4-octene could afford the desired product **48** in excellent diastereoselectivity, albeit in diminished yield.

Table 3. Representative Alkene Substrate Scope.[a]



[a] Standard reaction conditions, Selectfluor (200 mol %). Product ratios were determined for crude mixtures based on ^{1}H NMR. Isolated yields were for the major isomer. [b] 1.0 equiv. BF_3•Et_2O was added. [c] Selectfluor (120 mol %). [d] LiI (20 mol %), Selectfluor (150 mol %).

The high regioselectivity observed for both activated and unactivated olefins is noteworthy, particularly for unactivated olefins, a difficult class of olefins in intermolecular olefin oxyamination.[23] An intriguing regioselectivity feature concerning the aliphatic alkene substrates arose with the observation of the opposite regioisomer (relative to N vs. O additions) being the major isomer compared with the styrene derivatives (Figure 1). For the aliphatic olefins, the addition to the iodonium **E** is controlled by electronic bias (product **23**), whereas the addition to the iodonium intermediate **F** is controlled by steric bias (product **24** vs. **46**). In both cases, the nitrogen atom of **2** served as the initial nucleophile for the regiochemical-determining step. The catalytic utilization of an iodonium intermediate for regiochemical control, in this regard, offers an interesting avenue for regioselectivity in alkene difunctionalization reactions.[11] Furthermore, we also demonstrated aliphatic alkene derived from Ibuprofen, (L)-prolinol, and (1S)-(-)-Camphanic acid could afford the corresponding heterocyclic products **49**, **50**, and **51** in excellent yields and regioselectivities.

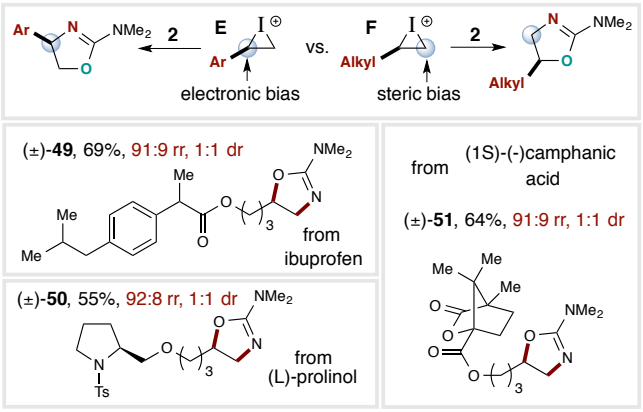


Figure 1. Regiochemical control and functional group compatibility.

To probe the reaction mechanism, we conducted a stereospecificity test with both *trans*- and *cis*-β-methylstyrene (Figure 2a). The retention of stereochemistry for *cis*-β-methylstyrene suggests the intermediacy of an iodonium since radical or cationic pathways will likely result in the *trans*-oxazoline **3** as the major product.[24] The erosion in stereospecificity is most likely due to erosion of alkene starting material stereochemistry as control reaction in the absence of the nucleophile revealed recovery of 85% of the trans-β-methyl styrene only.[25] Although the yields for the 1,2-disubstituted 4-octene are low, the product diastereoselecltivity indicates no loss of stereospecificity. Furthermore, cis-4-octene in a control reaction also revealed no isomerization of starting material. In addition, we presynthesized the iodo intermediate **53**, which also participated in the reaction to afford the same level of yield and regioselectivity, indicating the viability of **53** as a catalytic intermediate (Figure 2b).[26]

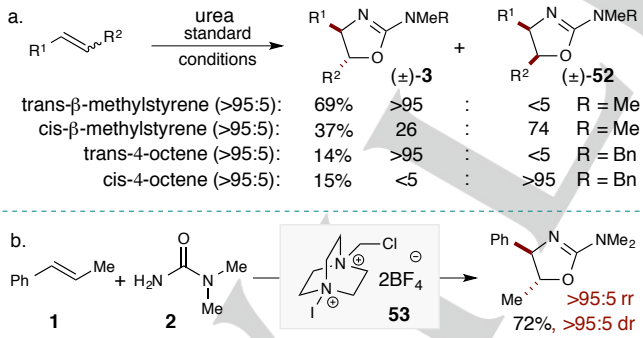


Figure 2. Mechanistic studies.

In conclusion, we have demonstrated a novel iodide-catalyzed formal [3+2] cycloadditions of alkenes and ureas. The high regio- and diastereoselectivity observed in these reactions are compelling. Notable features of this reaction include rendering iodide as a catalyst and urea as an oxyamination reagent for intermolecular olefin aminooxygenation. Based on this catalytic strategy, an important class of N- and O-containing heterocycles with useful bioactivities can be easily accessed. Mechanistic studies suggest the catalytic involvement of an iodonium intermediate. Finally, the asymmetric variant and the refinement of oxidant for this reaction are currently being investigated in our laboratory.

Acknowledgements

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Keywords: Olefin Aminooxygenation • Iodide Catalysis • Regiocontrol • Alkene Difunctionalization • Oxazoline Synthesis

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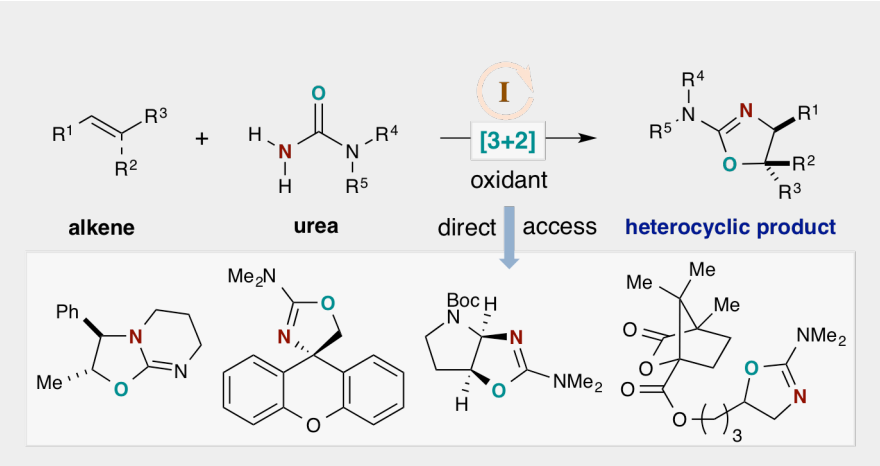

Alkene urea formal [3+2] cycloaddition: An iodide-catalyzed olefin aminooxygenation reaction is described. This reaction enables the direct coupling of urea with both activated and unactivated alkenes to afford a range of interesting heterocyclic structures with great regio- and stereochemical control.

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Regioselective Formal [3+2] Cycloadditions of Ureas with Activated and Unactivated Olefins for Intermolecular Olefin Aminooxygenation