Communication

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Metal- and Reagent-Free Intramolecular Oxidative Amination of Tri- and Tetrasubstituted Alkenes

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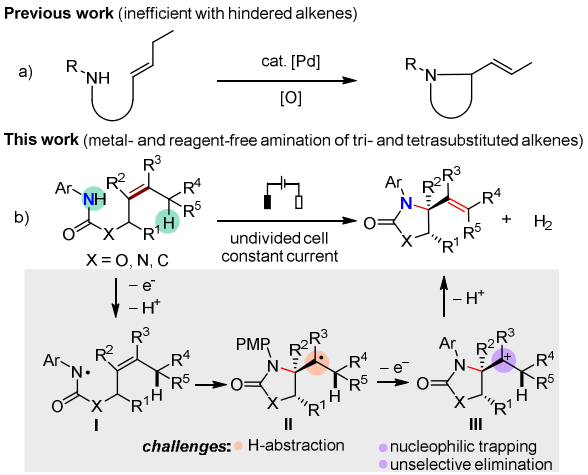
Supporting Information Placeholder

ABSTRACT: A metal- and reagent-free, electrochemical intramolecular oxidative amination reaction of tri- and tetrasubstituted alkenes has been developed. The electrosynthetic method proceeds through radical cyclization to form the key C–N bond, allowing a variety of hindered tri- and tetrasubstituted olefins to participate in the amination reaction. The result is the efficient synthesis of a host of alkene-bearing cyclic carbamates and ureas and lactams.

Allylic amines are important synthetic building blocks that can be converted into a diverse range of products through the manipulation of the amino as well as alkenyl moieties.[1] Recently, there has been considerable interest in preparing these compounds through the cross-coupling between a N–H bond and an allylic C–H bond, which allows for an efficient route from easily available starting materials.[2] Particularly, the aza-Wacker type cyclizations, which is often catalyzed by a palladium species, allows the easy access to alkene-containing *N*-heterocycles (Scheme 1a).[3] A number of excellent recent studies have reported successful aza-Wacker cyclizations under mild conditions and with molecular oxygen as the terminal oxidant.[4] Despite this progress, reported methods are generally not efficient with multisubstituted alkenes and oxidative amination of tri- and tetrasubstituted olefins remains challenging.

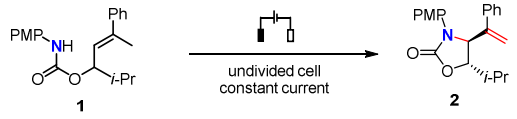
Nitrogen-centered radical (NCR) intermediates have attracted considerable interest from organic chemists due to their ability to cyclize with alkenes of diverse steric properties, leading to the formation of new C–N bonds.[5] The synthetic utility of these reactive species has been further boosted by the emergence of various new methodologies, particularly those involving single electron transfers, that greatly facilitated their preparation.[5b,c] We have been involved in developing sustainable C–N bond-forming reactions by employing electrochemically generated NCRs.[6,7] Based on these results, we envisioned an electrochemical amination reaction (Scheme 1b).[8] The anodic activation of the amidyl N–H bond in an alkene-tethered amide could lead to the generation of a NCR intermediate **I**,[9] which could then readily undergo intramolecular cyclization with the alkenyl moiety to give the carbon-centered radical **II**. Oxidation of this latter C-radical followed by the loss of a proton would afford the cyclic allylamine product. The challenge of this approach lies in its requirement for the efficient and regioselective installation of an alkenyl moiety in the absence of a metal-based catalyst. The C-radical **II** is prone to reduction through H-abstraction,[7a,10] whereas its derived cation **III** can be trapped by a nucleophile,[8a,b,11] or participate in nonselective/undesired proton elimination.[12] Herein, we report the successful development of an intramolecular oxidative amination of the challenging tri- and tetrasubstituted alkenes through electrochemical oxidation (Scheme 1b).[13] Advantageously, this process proceeds in a metal-[14] and reagent-free[15] fashion to provide functionalized cyclic carbamates and ureas and lactams.

Scheme 1. Intramolecular Oxidative Amination of Alkenes



We first identified the optimal reaction conditions for the cyclization of carbamate **1** bearing a trisubstituted olefin, which involved constant-current electrolysis using a reticulated vitreous carbon (RVC) anode and a Pt plate cathode, in an undivided cell containing a mixed electrolyte solution of Et_4NPF_6 in dimethylacetamide (DMA) and acetic acid (40:1). Under these conditions, the desired cyclic carbamate **2** was isolated in 82% yield (Table 1, entry 1). Particularly noteworthy is the fact that the regeneration of the C–C double bond occurred regioselectively at the terminus, instead of favoring the formation of the more thermodynamically stable enamine derivative (a tetrasubstituted alkene). Despite that the redox potentials ($E_{p/2}$ vs SCE in MeCN) of **1** (1.23 V) and **2** (1.39 V) were close to each other, over-oxidation was not observed. Conducting the electrolysis without AcOH (entry 2),[16] or in other solvents such as DMF (entry 3) or MeCN (entry 4), dramatically decreased product formation. In comparison, slightly reduced but still acceptable yields were obtained when the reaction conditions were modified in one of the following manners: lowering the concentration of Et_4NPF_6, changing the electrolyte to nBu$_4$NBF$_4$ or Et_4NOTs(entry 5), switching to a platinum plate anode (entry 6) with a surface

Table 1. Optimization of Reaction Conditions[a]



1 2

Entry	Conditions	Yield%[b]
1	DMA/AcOH (40:1), Et_4NPF_6 (1 equiv), 110 °C, 10 mA	83 (82)[c]
2	entry 1 but no AcOH	41
3	entry 1 but MeCN as solvent	10
4	entry 1 but DMF as solvent	50
5	entry 1 but Et_4NPF_6 (0.5 equiv) or nBu_4NBF_4 or Et_4NOTs as electrolyte	71–76
6	entry 1 but Pt plate (1 cm x 1 cm) as anode	75
7	entry 1 but 20 mA	75[d]
8	entry 1 but 5 mA	25[e]
9	entry 1 but reaction at RT	45

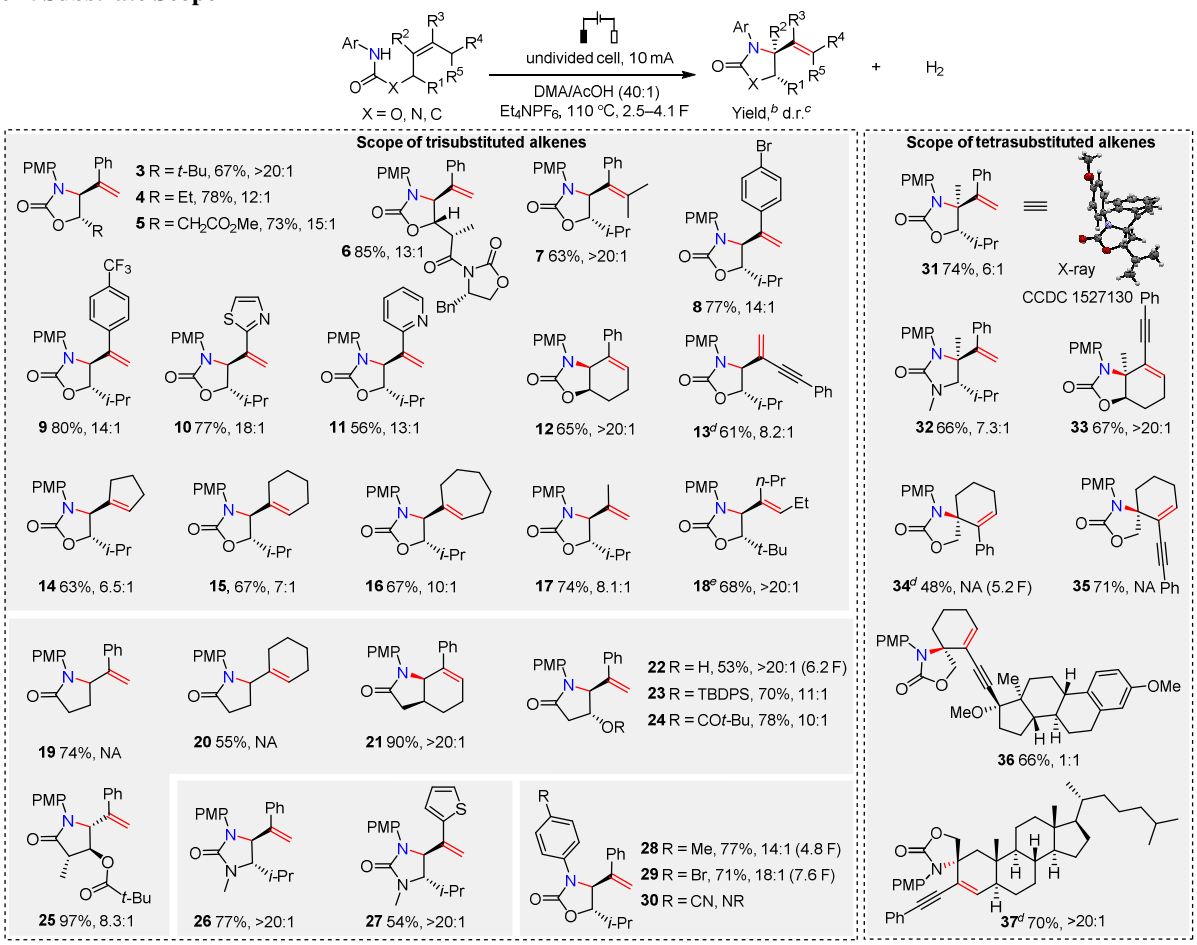
[a]Reaction conditions: RVC anode (100 PPI, 1 cm x 1 cm x 1 cm), Pt cathode (1 cm x 1 cm), **1** (0.3 mmol), solvent (4 mL), argon, 2.4 h (3 F). [b]Yield of the major diastereomer determined by ^{1}H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]Isolated yield. [d]Reaction time = 1.2 h. [e]Reaction time = 4.8 h. PMP = *p*-methoxyphenyl.

area much lower than that of the RVC anode, or adjusting the current to 20 mA (entry 7). However, performing the electrolytic amination at 5 mA (entry 8) or at RT (entry 9) greatly diminished the yield.

We next explored the substrate scope of the electrolytic amination reaction using a host of carbamates carrying various trisubstituted alkenyl moieties (Scheme 2, **3**–**18**). The reaction was demonstrated to be compatible with a diverse range of (hetero)aryl- (**3**–**12**), alkynyl- (**13**) and alkyl- (**14**–**18**) substituted olefins. The cyclic carbamate products were produced with good to high diastereoselectivity and proton elimination proceeded regioselectively at the distal carbon relative to the newly formed *N*-heterocycle, leading to an allylamine moiety regardless of the substitution pattern of the starting alkene. Both terminal and internal olefins, including a tetrasubstituted one (**7**), could be achieved.

Further studies revealed that unsaturated amides (**19**–**25**) and ureas (**26**–**27**) were also viable substrates (Scheme 2). Carbamates bearing less electron-rich N-aryl rings, such as *p*-Me-Ph (**28**) and *p*-Br-Ph (**29**), also underwent smooth cyclization with satisfactory yields, albeit in reduced current efficiency. However, no reaction occurred when the substrate contained the highly electron-withdrawing *p*-CN-Ph group (**30**). The increased oxidation potentials[17] of these substrates tipped the reaction toward solvent decomposition. Furthermore, a variety of functional groups were found to be well-tolerated, including ester (**5**, **24**–**25**), imide (**6**), arylbromide (**8**), thiazole (**10**), pyridine (**11**), thiophene (**27**), alkyne (**13**), alcohol (**22**) and silyl ether (**23**).

Scheme 2. Substrate Scope[a]

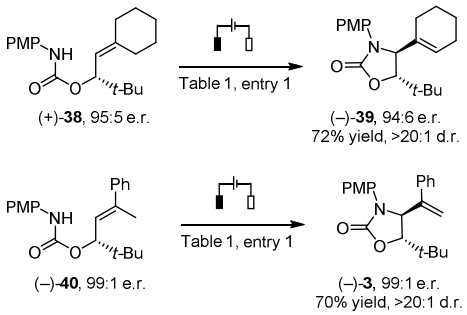


[a]Reaction conditions from Table 1, entry 1 were used unless otherwise noted. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Reaction at 130 °C. [e]*E*/*Z* = 5:1. TBDPS = *tert*-butyldiphenylsilyl. NR = no reaction.

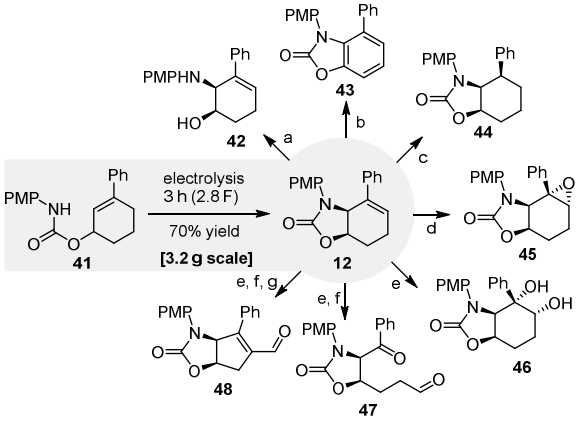
One major advantage of the electrochemical method lies in its efficient amination of sterically demanding tetrasubstituted alkenes.[18] As summarized in Scheme 2, both acyclic (**31**–**32**) and cyclic (**33**–**37**) olefins, including two that contained a steroid-based core structure (**36**–**37**), were shown to readily react to afford desired products with aza-quarternary stereocenters.

The facile preparation of enantioenriched cyclic carbamates from easily available enantioenriched allylic alcohols[19] lent further support to the synthetic utility of the intramolecular amination reaction in the current study (Scheme 3). As examples, subjecting (+)-**38** and (−)-**40** to the standard electrolysis conditions resulted in the stereoselective formation of (−)-**39** and (−)-**3**, respectively, without any observable loss of the enantiomeric ratio.

Scheme 3. Cyclization of Enantioenriched Carbamates



Scheme 4. Gram-Scale Synthesis and Product Transformations



Reaction conditions. a) KOH, EtOH/H_2O, reflux, 82%. b) Copper (II) 2-ethylhexanoate, IBX, DMSO/TFA, 110 ℃, 64%. c) H_2, Pd/C, MeOH, RT, 93%. d) *m*-CPBA, CH_2Cl_2, RT, 83%. e) OsO_4, NMO, RT, 84%. f) $Pb(OAc)_4$, RT, 91%. g) Piperidine, AcOH, 40 ℃, 84%.

Two additional advantages of our electrolytic amination process include its easy scalability and the synthetic value of the generated alkene-bearing N-heterocycles. For instance, the cyclization of 3.2 grams of **41** produced the corresponding product **12** in 70% yield (Scheme 4), showing no appreciable loss in product formation efficiency in comparison to the same reaction conducted on a 0.1-gram scale. The hydrolysis of the carbamate moiety in **12** afforded allylamine **42**, whereas the same starting compound could also be converted to benzimidazolidinone **43** via copper-catalyzed dehydrogenative aromatization. Furthermore, the alkene C–C double bond in **12** was amenable to a variety of chemical transformations such as hydrogenation, epoxidation and dihydroxylation to furnish saturated carbo-cycle **44**, epoxide **45** and vicinal diol **46**, respectively.[20] Compound **46** could be converted to ketoaldehyde **47** through the oxidative cleavage of its diol moiety, and further to ketoaldehyde **48** by aldol condensation.[21]

In summary, we have successfully developed an efficient intramolecular oxidative amination reaction of challenging tri- and tetrasubstituted alkenes. Our electrosynthetic method is broadly compatible with a wide range of carbamate, amide, and urea substrates, can be easily scaled up, and provide access to various functionalized N-heterocycles with great synthetic values.

ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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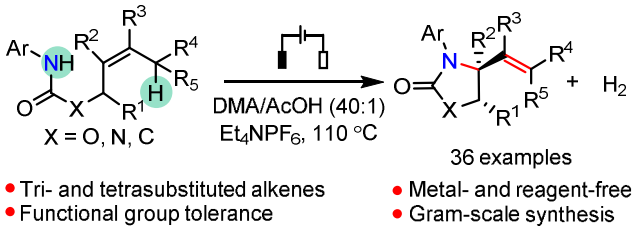
Ar
NH
R2
R3
R4
R5
H
O
X
R1
X = O, N, C
DMA/AcOH (40:1)
Et4NPF6, 110 °C
N
+
H2
36 examples
Tri- and tetrasubstituted alkenes
Functional group tolerance
Metal- and reagent-free
Gram-scale synthesis