Metal-free Intermolecular Allylic C-H Amination of Alkenes Using Primary Carbamates

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ABSTRACT: The allylic C-H amination of alkenes is a powerful method for the regioselective formation of new C-N bonds. Though many methods for introducing a wide range of nitrogen groups intermolecularly have been developed, few of these utilize carbamates, which are an important class of bioactive compounds and are commonly used as protecting groups for free amines. Here, we report a convenient metal-free protocol for intermolecular allylic C-H amination using unactivated primary carbamates as the nitrogen source. A sterically hindered NHC-selenium catalyst was found to be critical to obtaining high yields. A wide range of trisubstituted and 1,1-disubstituted alkenes were regioselectively aminated, including terpenoid natural products. A range of common carbamate protecting groups such as Cbz, Teoc, and Alloc could be successfully incorporated into alkene substrates. Additionally, trifluoroacetamide was shown to be a viable nitrogen source. The observed regio- and stereoselectivities can be explained by a sequential ene reaction/[2,3]-sigmatropic rearrangement mechanism in which cis C-H bonds are preferentially activated but subsequent rearrangement results in selective formation of trans alkene products.

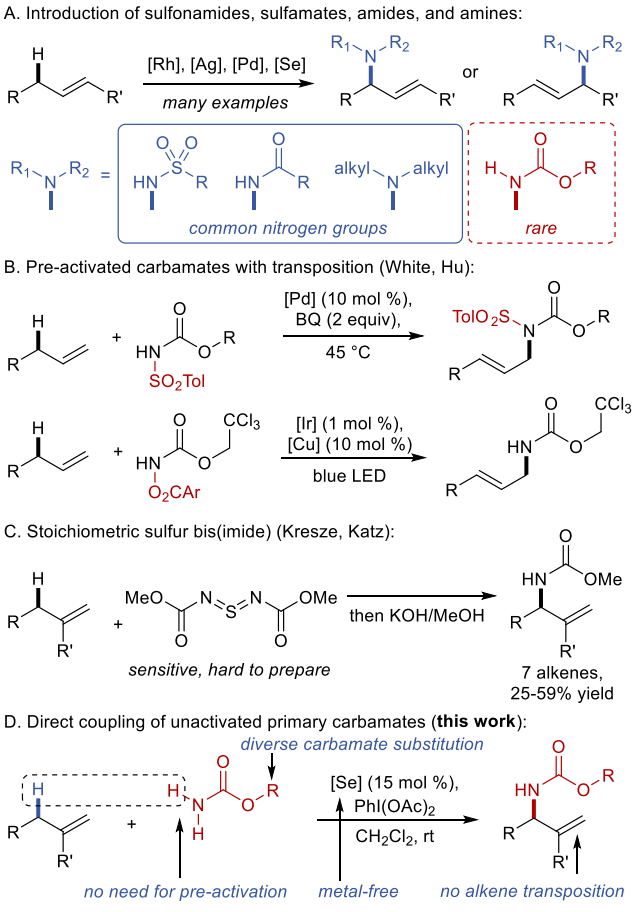
INTRODUCTION

The development of new methods for the incorporation of nitrogen functionality into organic molecules is an important and longstanding synthetic problem, driven by the biological and medicinal importance of nitrogen-containing compounds. Installation of nitrogen groups via direct C-H amination reactions provides an especially direct and efficient solution to this problem.[1-6] In addressing the critical challenge of how to control C-H bond selectivity in intermolecular C-H amination reactions, the alkene functional group has proven to be a useful and ubiquitious handle for functionalization, owing to the presence of relatively weak allylic C-H bonds. As such, a wide variety of catalytic methods for selective amination at the allylic position have been developed.[7] Intermolecular delivery of nitrogen groups via allylic C-H amination reactions of alkenes has been well established using a variety of transition metal and main group catalysts, allowing controlled synthesis of allylic sulfonamides,[8-18] amides,[19-22] and more recently alkylamines[23-29] (Scheme 1A).

Despite this progress, the ability to use simple primary carbamates as a nitrogen source in intermolecular allylic C-H amination reactions has remained surprisingly underexplored, especially considering the early role they played in the development of intramolecular C-H amination.[30-32] In pioneering work, White and co-workers showed that *N*-tosylcarbamates could be used in a Pd-catalyzed allylic C-H amination reaction (Scheme 1B).[33-35] The added sulfonyl substituent was found to be necessary to lower the pKa enough to achieve the desired reactivity. More recently, Hu has reported that allylic trichloroethyl carbamates can be generated from alkenes using an Ir-photocatalyzed method.[36-37] However, this reaction required the preparation of a pre-activated *N*-carboxycarbamate as the nitrogen source. Additionally, both reactions resulted in alkene transposition as a consequence of their mechanisms.

In a lone example[38] of an intermolecular allylic C-H amination using carbamates without alkene transposition, Kresze showed that an isolated sulfur bis(imide) could be used to install a carbamate group (Scheme 1C).[39,40] However, this bis(imide) reagent was challenging to prepare and its use was only demonstrated with a small set of trisubstituted alkene substrates in moderate yields.

Scheme 1. Intermolecular Allylic C-H Aminations



Addressing the dearth of methods for allylic C-H activation using simple carbamates would constitute a major advance given the key role that carbamates occupy in drug discovery, medicinal chemistry, agricultural chemistry, and polymer science.[41-43] Perhaps most importantly, carbamates are extensively used as protecting groups for amines, owing to their ease of installation and their ability to offer a variety of facile deprotection strategies.[44] Direct installation of a range of orthogonal carbamate protecting groups would greatly increase the synthetic flexibility of the allylic C-H amination approach. Herein, we report a new metal-free catalytic C-H amination reaction that utilizes a variety of simple primary carbamates as nitrogen sources without the need for pre-activation. This reaction does not result in allylic transposition and offers predictable regioselectivity for a variety of alkene substrates.

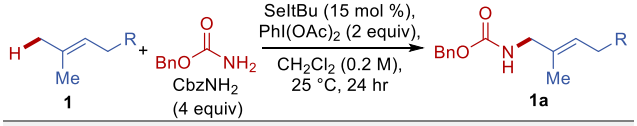
We and others have recently demonstrated allylic C-H amination reactions catalyzed by selenium complexes.[8-11,45] Our protocol enabled regioselective C-N bond formation on a wide variety of complex alkene substrates. Importantly, this metal-free reaction directly employed a wide range of primary sulfonamides and sulfamates as nitrogen sources without the need for separate synthesis of a nitrenoid precursor. We imagined that development of a similarly broad C-H amination using primary carbamates would address an important need in the construction of nitrogen-containing compounds. Our original catalytic system relied on the *in situ* formation of an *N*-sulfonyl iminoiodinane from $PhI(OAc)_2$. Though iminoiodinanes derived from carbamates have not been prepared, we proposed that we might be able to rely on *in situ* formation of these species, as has been invoked in various intramolecular C-H amination protocols.[30-32] However, we recognized that the resulting selenium bis(imide) intermediate was likely to be less electrophilic than the analogous sulfonamide-derived species, which could present challenges in achieving desired reactivity with the mildly nucleophilic alkene substrates.

RESULTS AND DISCUSSION

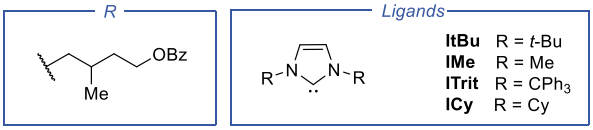
We began our investigation by subjecting a mixture of citronellol benzoate (**1**) and benzyl carbamate ($CbzNH_2$) to iodobenzene diacetate ($PhI(OAc)_2$) and a catalytic amount of either $SePCy_3$ or SeIMe, as these two catalysts had previously given the best results for the allylic amination with sulfamates and sulfonamides. Encouragingly, we did observe the desired C-H amination product **1a** as a single regioisomer. However, the yield of **1a** obtained using either of these catalysts was low (~30%, entries 3 and 4). Since the structure of the ligand on selenium had previously been shown to play a key role in the reactivity of the catalytic system, we screened a variety of other phosphine selenides and selenoureas as catalysts (entries 3-6). Other phosphine ligands were generally found to be ineffective for this protocol. However, we found that the use of sterically demanding NHC ligands improved the yields, with the bulky ItBu ligand giving the highest yield (74%, entry 1). Dichloromethane was found to be the optimal solvent, but we observed that toluene could also be used with a moderate reduction in yield (entries 7, 8). The choice of oxidant proved critical for high conversion to the desired product; other hypervalent iodine sources were not effective (entries 9, 10).

Having developed an optimal set of reaction conditions, we next evaluated these conditions using a variety of alkene substrates (Scheme 2). Trisubstituted alkenes were always aminated on the more substituted end of the C=C bond, and all gave exclusively (*E*)-alkene products (**1-26**). A variety of functional groups, including esters, ketones, ethers, silyl ethers, nitriles, acetals, and heteroarenes are all well-tolerated under these reaction conditions. The reaction could be run on 5 mmol scale with no reduction in yield. Aryl (**2**) and alkyl halides (**11**) could also be used, allowing the possibility of further functionalization. For substrates with multiple alkenes, amination occurred exclusively at the more electron rich alkene (**8, 13**). Allylic ether groups were tolerated on trisubstituted alkenes (**14**) but benzoate groups in this same position resulted in no reaction (**15**), presumably due to the increased inductive withdrawing ability of this group. Interestingly, both (*E*)- and (*Z*)-trisubstituted alkene **21** gave exclusively (*E*) products but with drastically different regioselectivities. The highly selective transformation of (*Z*)-**21** to (*E*)-**21a** reveals a complex interplay between amination selectivity and *E*/*Z* interconversion in this unique mechanism (see below).

Table 1. Optimization of Reaction Conditions



entry	variation from standard conditions	yield[a]
1	none	74%
2	35 °C *instead of* 25 °C	65%
3	$SePCy_3$ *instead of* SeItBu	32%
4	SeIMe *instead of* SeItBu	29%
5	SeICy *instead of* SeItBu	<5%
6	SeITrit *instead of* SeItBu	46%
7	Toluene *instead of* CH_2Cl_2	48%
8	MeCN *instead of* CH_2Cl_2	23%
9	Dess-Martin Periodinane *instead of* $PhI(OAc)_2$	9%
10	PhIO *instead of* $PhI(OAc)_2$	<5%
11	2 equiv of $CbzNH_2$ *instead of* 4 equiv	55%

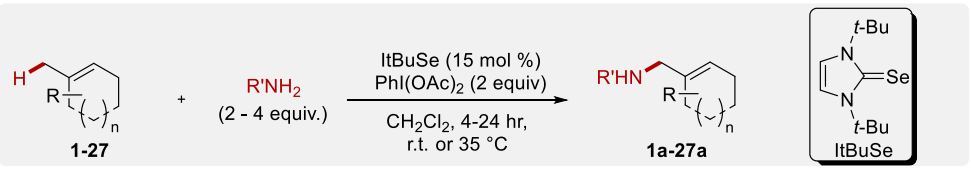


[a]Isolated yield

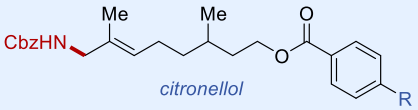
Additionally, several 1,1-disubstituted alkenes were also suitable substrates for this C-H functionalization. Axial C-H bonds were aminated with excellent diastereoselectivity (**28**). Amination was found to occur at primary, secondary, and tertiary positions (**31-33**), following the same order previously observed for sulfonamides and sulfamates (2°>3°~1°).[8] In order to probe the feasibility of this protocol for late-stage site selective amination, we subjected several terpenoid scaffolds to the reaction conditions (**22-27**). Gratifyingly, we found that many terpenoids bearing tri- and 1,1-disubstituted alkenes were readily aminated using this protocol. Reflecting the less electron withdrawing nature of the carbamates relative to sulfonamides, terminal alkenes and 1,2-disubstituted alkenes were not reactive under these conditions, giving quantitative recovery of the alkene.

We next evaluated the scope of carbamates that could be coupled under these conditions. Simple alkyl substitution was readily tolerated and gave good yields of the products. Several known carbamate protecting groups that are removable under

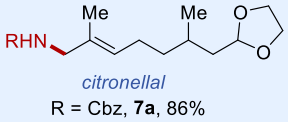
Scheme 2. Alkene and Carbamate Substrate Scope for Allylic C-H Amination



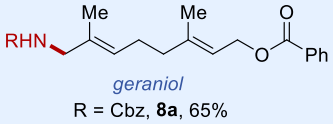
trisubstituted alkenes



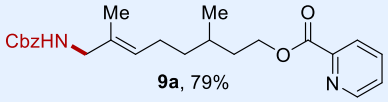
R = H, **1a**, 74% (71%, 5 mmol scale)
R = I, **2a**, 73%
R = CN, **3a**, 89%
R = Ac, **4a**, 84%
R = NO_2, **5a**, 73%
R = OMe, **6a**, 81%



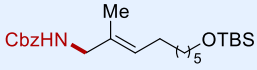
R = Cbz, **7a**, 86%
R = CO_2Me, **7b**, 65%



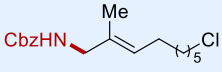
R = Cbz, **8a**, 65%



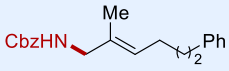
9a, 79%



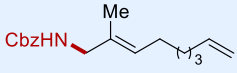
10a, 70%



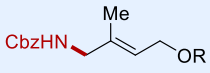
11a, 80%



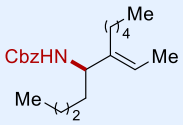
12a, 98%



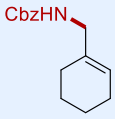
13a, 68%



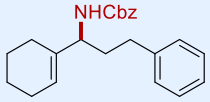
R = TBS, **14a**, 66%[a,b]
R = Bz, **15a**, 0%



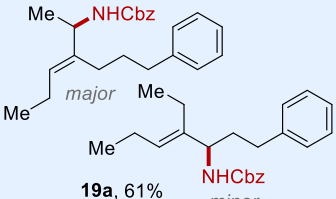
16a, 79%



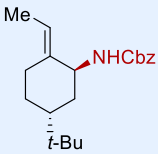
17a, 49%
rr = 3.8:1



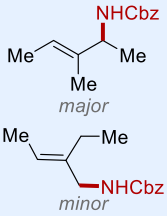
18a, 46%
rr = 1.4:1



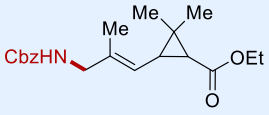
19a, 61%
ratio = 1.4:1



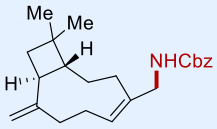
20a, 69%
dr = 1.4:1



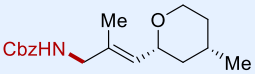
from (*Z*)-**21**: **21a**, 88%[a]
ratio = 8.3:1
from (*E*)-**21**: **21a**, 65%[a]
ratio = 1.2:1



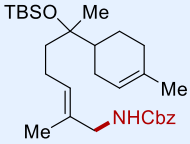
ethyl chrysanthemate
22a, 69%[a]



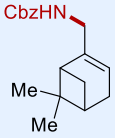
β-caryophyllene
23a, 62%



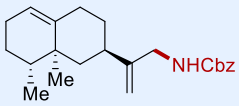
rose oxide
24a, 75%[a]



bisabolol
25a, 60%[a]
dr = 1:1

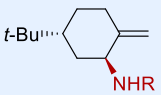


α-pinene
26a, 74%[a]

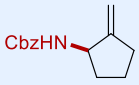


valencene
27a, 51%[a]
rr = 2.3:1

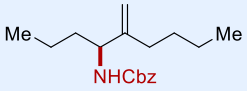
1,1-disubstituted alkenes



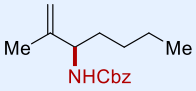
R = Cbz, **28a**, 87%
dr = 10:1
R = CO_2Me, **28b**, 67%
dr = 14.3:1



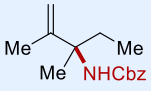
29a, 52%[a]



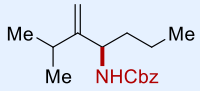
R = Cbz, **30a**, 63%
R = CO_2Me, **30b**, 80%



R = Cbz, **31a**, 83%
rr = 4.2:1
R = CO_2Me, **31b**, 75%
rr = 3:1

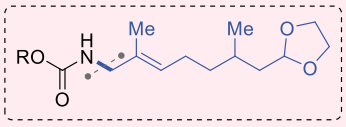


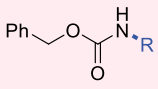
32a, 62%[a]
rr = 1.4:1



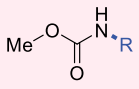
33a, 58%
rr = 2:1

Carbamates[c]

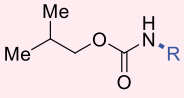




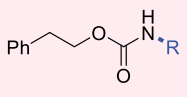
Cbz
7a, 86%



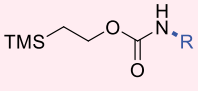
7b, 65%



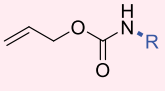
7c, 73%



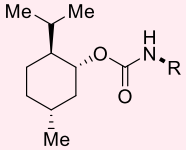
hZ
7d, 76%



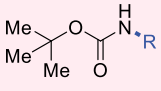
Teoc
7e, 62%



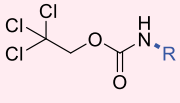
Alloc
7f, 48%



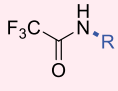
7g, 77%



Boc
7h, 35%



Troc
7j, 11%



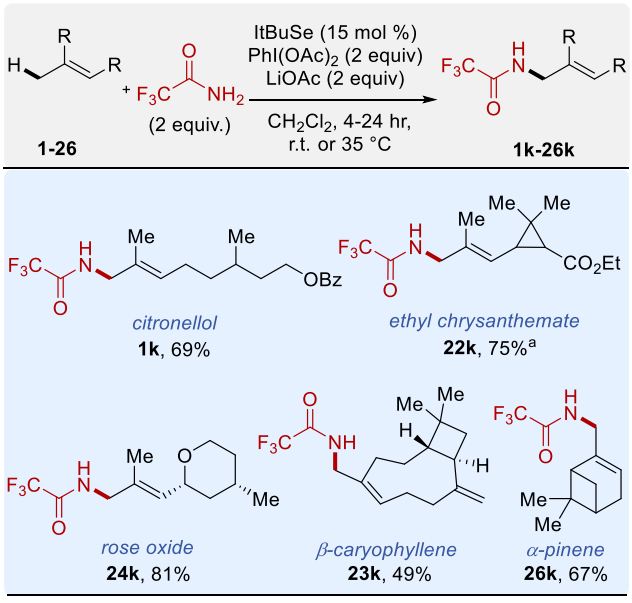
TFA
7k, 19% (68%)[d]

[a]Standard conditions using 25 mol % catalyst loading, [b]Reaction was run for 72 hours [c]2 equiv carbamate except Cbz [d]with LiOAc (2 equiv)

diverse conditions, such as Teoc, Alloc and homobenzyl (hZ) could also be used. Bulky chiral carbamates such as menthyl carbamate were also shown to be competent reaction partners. Pleasingly, all carbamates besides Cbz provided high yields using only 2 equivalents of the carbamate. Consistent with a non-nitrene mechanism, intramolecular C-H amination of the carbamate was never observed. Unfortunately, Boc and Troc carbamates gave relatively poor yields.

Having successfully developed this amination protocol using a range of carbamates as nitrogen sources, we considered whether other easily-deprotected ammonia surrogates could be employed. Since it is easily obtained and readily cleaved under mildly basic conditions, trifluoroacetamide is an appealing nitrogen source. Initial evaluation of trifluoroacetamide under our standard catalytic conditions afforded only 19% yield of the desired amination product. However, we found that the addition of lithium acetate greatly improved the desired reactivity, allowing us to obtain 68% of the allylic amide product. In our previous work, basic additives have been shown to improve the yield, presumably to scavenge acidic byproducts of the reaction.[10] To test the generality of this protocol, we screened a few natural terpene scaffolds using trifluoroacetamide as the nitrogen source and obtained moderate to good yields of the desired amination products in every case (Scheme 3). Other amides were not suitable coupling partners under these conditions, presumably due to competing Hofmann rearrangement (see SI for examples).[46]

Scheme 3. Trifluoroacetamide C-H Aminations



[a]Standard conditions using 25 mol % catalyst loading

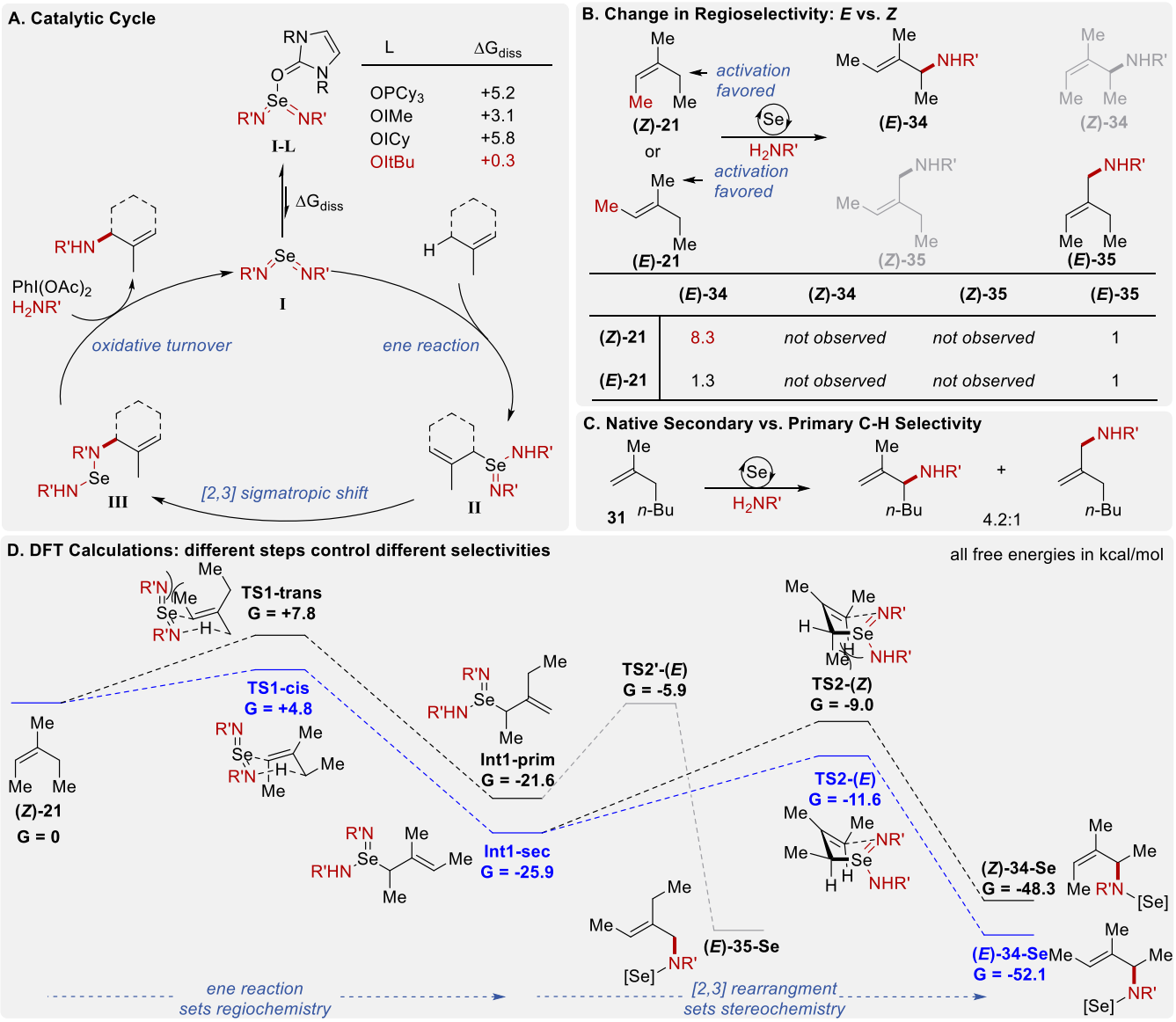
The regioselectivity observed upon amination of the alkenes in Scheme 2 is generally consistent with our previously reported selenium-catalyzed amination protocol using sulfamates and sulfonamides, and can be explained by considering the mechanism in Scheme 4A. Reaction of the selenium complex with *in situ* generated iminoiodinane affords selenium bis(imide) **I**, which then undergoes an asynchronous ene reaction by attack of the selenium on the less substituted end of the alkene. Subsequent [2,3]-sigmatropic rearrangement and catalyst reoxidation complete the catalytic cycle.

Previous mechanistic studies have indicated that the selenium bis(imide) can reversibly coordinate to the oxidation product of the NHC ligand.[8] Though the exact role of the ligand is still unclear, we hypothesize that the improved performance of the ItBu-derived catalyst may be due to steric inhibition of O=ItBu binding to the key bis(imide) intermediate. To test this, we performed DFT calculations on the energy required to dissociate the oxidized ligands from the selenium bis(imide) I (Scheme 4a). Binding of O=ItBu to selenium is 3-5 kcal/mol less exergonic than any of the other oxidized ligands, indicating that more facile dissocation of O=ItBu lowers the overall barrier for entry into the catalytic cycle. The significant difference in dissociation energy between O=ICy and O=ItBu can be attributed to the ability of the cyclohexyl groups to easily rotate away from the Lewis basic oxygen, as is observed in the corresponding A values of Me, Cy, and tBu (1.8, 2.2, and >5 kcal/mol respectively).

To shed more light on the effect of alkene geometry on the outcome of the amination reaction, we examined the amination of the *E* and *Z* isomers of trisubstituted alkene **21** more closely (Scheme 4B). Four possible products can be formed: namely, amination at either the secondary (**34**) or the primary (**35**) position, and both products could be formed as *E* or *Z* isomers. Amination of both (*Z*)-**21** and (*E*)-**21** only gave 2 of the 4 possible isomers, but in different ratios: (*Z*)-**21** preferentially gave the secondary carbamate product (*E*)-**34** in an 8.3:1 ratio whereas (*E*)-**21** gave a nearly equal mixture of (*E*)-**34** and (*E*)-**35**. For comparison, the native preference for secondary C-H amination vs primary can be obtained from the reaction of 1,1-disubstituted alkene **31**, which gives a ratio of 4.2:1 favoring secondary activation (Scheme 4C). The increase in secondary C-H selectivity for (*Z*)-**21** (and corresponding decrease in selectivity for (*E*)-**21**) reveals a preference for activation of the C-H bond *cis* to the non-hydrogen substituent on the less-substituted end.[47] However, this must be reconciled with the fact that ultimately the *E* products are exclusively formed.

These results can be explained by consideration of the ene/[2,3]-rearrangement mechanism, with each step independently responsible for one mode of selectivity (Scheme 4D). The initial ene reaction dictates which C-H bond is cleaved, which determines whether regioisomeric product **34** or **35** is eventually formed. The final alkene geometry (*E* vs *Z*), however, is only determined by the [2,3]-sigmatropic rearrangement step when the alkene is transposed to its original position. To confirm this analysis, DFT calculations[48] were performed on the reaction mechanism for amination of substrate **(*Z*)-21** and were found to be consistent with this analysis and with the experimental results. For the ene reaction, we have previously shown that an endo transition state is preferred,[8] i.e. the non-reacting imido group adopts a pseudoaxial position. Examination of the two possible endo ene transition states (**TS1-cis** and **TS1-trans**) reveals that **TS1-trans** incurs an added steric clash between the spectator imido substituent and the equatorial methyl group, which is avoided in **TS1-cis**, thus resulting in a preference for activation of the cis substituent. Indeed, **TS1-cis** is calculated to be significantly lower in energy, leading to preferential formation of allylic selenium species **Int1-sec**. Since the activation barrier for the retro-ene reaction is calculated to be ~30 kcal/mol, this step irreversibly sets the observed regioselectivity. After the ene reaction, there are two possible transition states for the [2,3]-sigmatropic rearrangement, **TS2-(*E*)** and **TS2-(*Z*)**. The exclusive formation of *E* isomers can be explained by a strong preference for the methyl group to adopt the equatorial position in **TS2-(*E*)**, rather than the axial position in

Scheme 4. Mechanistic Considerations and DFT Calculations



TS2-(*Z*). Again, calculations indicate that **TS2-(*E*)** is lower in energy, giving **(*E*)-54** as the major product. A similar preference for *E* over *Z* in the transition states leading to product **35** is also observed (see SI for full details). Overall, this sequence of steps ends up directing C-H activation *cis* to the third alkene substituent and then isomerizing it to the *trans* position, rather than activating the *trans* position in the first place.

CONCLUSION

In conclusion, we have developed a metal-free allylic C-H amination reaction that uses simple primary carbamates as the nitrogen source. The protocol is convenient, requiring only the alkene, carbamate, inexpensive $PhI(OAc)_2$ and a sterically hindered NHC complex of selenium. A range of 1,1-disubstituted and trisubstituted alkenes were aminated in good yields and unique selectivity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and additional data (PDF)

Spectral characterization of materials (PDF)

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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 interest.

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