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Supporting Information Placeholder

ABSTRACT: Enamides represent bioactive pharmacophores in various natural products, and have become increasingly common reagents for asymmetric incorporation of nitrogen functionality. Yet the synthesis of the requisite geometrically defined enamides remains problematic, especially for highly substituted and Z-enamides. Herein we wish to report a general atom economic method for the isomerization of a broad range of N-allyl amides to form Z-di-, tri-, and tetrasubstituted enamides with exceptional geometric selectivity. This report represents the first examples of a catalytic isomerization of N-allyl amides to form non-propenyl disubstituted, tri- and tetrasubstituted enamides with excellent geometric control. Applications of these geometrically defined enamides towards the synthesis of cis vicinal amino alcohols and tetrasubstituted α-borylamido complexes are discussed.

INTRODUCTION: Enamides are stable, highly polarized, electron rich double bonds that are excellent substrates for incorporation of nitrogen functionality. They are commonly utilized in asymmetric hydrogenations,[1] cycloadditions,[2] cyclopropanations,[3] halo functionalizations,[4] heterocycle synthesis,[5] carbonyl and imine additions,[6] and transition metal mediated C-C bond formations.[7] In addition, enamides are important pharmacophores in various bioactive natural products that display a range of anti-cancer, anti-fungal, and cytotoxic properties (Figure 1).[8-9]

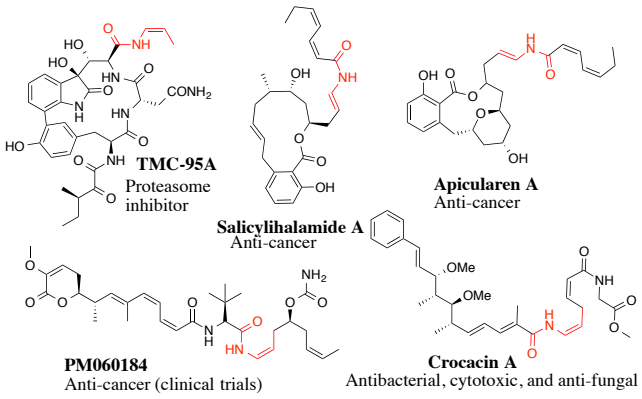


Figure 1: Bioactive Enamide Natural Products

Structure-activity relationship (SAR) studies have demonstrated the necessity of the enamide group, and of a specific enamide geometry, for excellent potency. Both the E, and less thermodynamically stable Z enamide isomers are widely represented within natural product scaffolds.

Traditional methods for the synthesis of enamides include acylation of imines, Curtius rearrangement of unsaturated acyl azides and condensation of amides with aldehydes. Unfortunately, these methods often give poor yields, low E:Z selectivities, and require harsh reaction conditions.[10] Attractive alternatives have been developed, including the metalation of ynamides[11] and the hydroamidation of terminal alkynes,[12] however these methods currently lack broad substrate scopes. Metalations generally require cyclic tertiary amides or carbamates, which are difficult to remove, and hydroamidations are limited to the synthesis of 1,2-disubstituted enamides. For the total synthesis of complex synthetic targets both methods have been largely overshadowed by the Cu and Pd catalyzed cross coupling of vinyl halides and triflates with amides,[13-16] which currently represents the most general protocol for the synthesis of geometrically defined enamides. However, these couplings still suffer from a number of limitations. The synthesis of the requisite geometrically defined vinyl halides or triflates, especially for highly substituted acyclic systems, is often problematic.[17] Furthermore, basic conditions, elevated temperatures and an excess of one coupling partner are often required.[10] Other nucleophilic positions, such as free alcohols, primary amides, and phenols, are usually protected as they can react competitively.[8c] Finally, additional cross coupling handles, such as boronic esters or acids, as well as vinyl or aryl halides and triflates are generally incompatible.

The transition metal catalyzed isomerization of N-allyl amides to enamides could provide an alternative, however, it routinely gives modest to poor E:Z selectivities.[18] This is not surprising, as reports of highly selective metal catalyzed isomerizations of *any* alkenes to give the thermodynamically less stable Z isomers,[19] as well as higher order trisubstituted alkenes are rare.[20] For enamides, there is a single report of forming the thermodynamically less stable Z-*propenyl* enamides selectively (>20:1 Z:E).[21] However, it

is limited to 4 examples with little functionality, and the authors note that the isomerization is entirely Z selective in "some" cases but do not comment on when this selectivity is diminished. Additionally there are no reports of forming higher order acyclic enamides, such as non *propenyl*, tri- or tetrasubstituted enamides with exceptional geometric control through a metal catalyzed isomerization of N-allyl amides. Herein we wish to report a remarkably general isomerization methodology for the synthesis of disubstituted (including both *propenyl* and *non propenyl*), tri-, and tetrasubstituted acyclic enamides with excellent geometric selectivity. The methodology is completely atom economic, displays excellent functional group tolerance, employs neutral conditions, requires easily accessible N-allyl amides, uses a commercially available catalyst, and can be run under atmospheric conditions (Figure 2). The conserved spatial orientation across all substitution patterns investigated likely arises from using a highly unsaturated ruthenium catalyst with *three* open coordination sites.[22] Preliminary evidence suggests that this unsaturation allows for amide coordination to enhance *both* reactivity and selectivity. In contrast, traditional isomerization methodologies towards enamides, and olefins in general, have largely focused on ligand design to create a steric bias for kinetic selectivities in the product-determining step.[18-20]

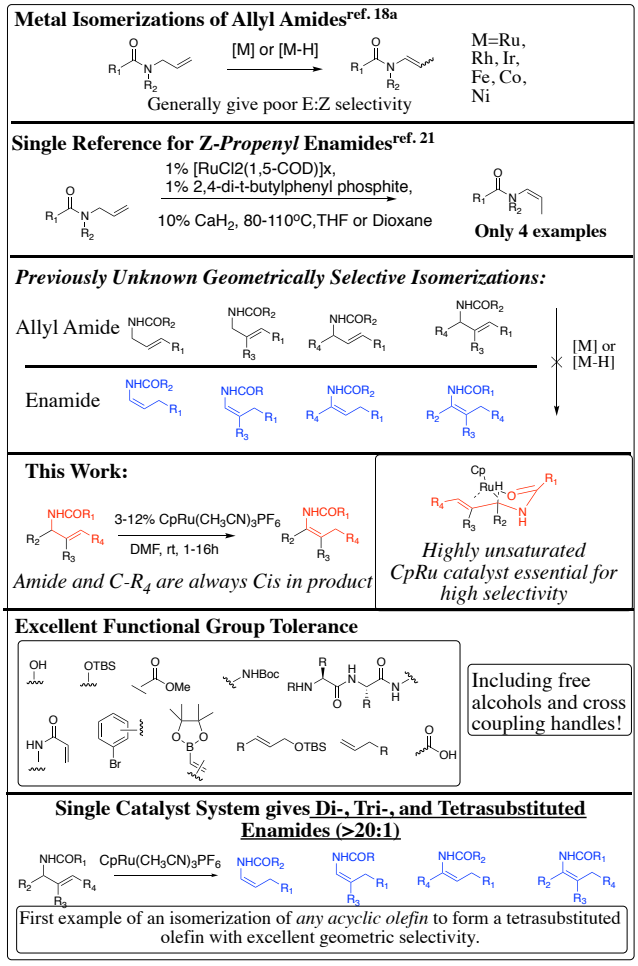
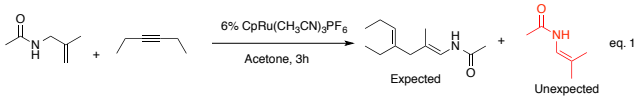


Figure 2: Isomerization of N-Allyl Amides

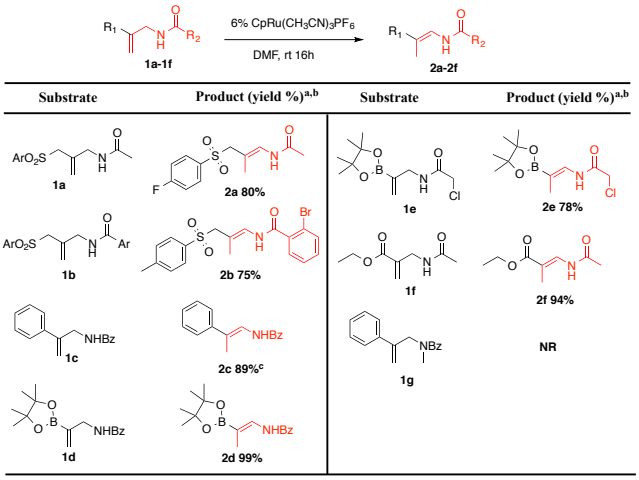
RESULTS AND DISCUSSION:

Our interest in the Ru catalyzed isomerization of N-allyl amides was initiated when we observed an enamide isomerization byproduct during our examination of more reactive disubstituted olefins in the alkene-alkyne coupling reaction shown below (eq.1).[23]



When an amide, instead of a carbamate-directing group, was used, an enamide product formed competitively. While the initial result was obtained in acetone we found DMF to give the highest conversions and yields. The $CpRu(CH_3CN)_3PF_6$ catalyst was found to be differential for this transformation. When we investigated substitution at R_1, we found the isomerization gave excellent geometric selectivities (>20:1) in all cases (Table 1). We were excited to see that vinyl boronic esters (**2d**,**2e**), and aryl halides (**2b**) were tolerated, since they are functional groups that would likely be reactive under Cu or Pd cross coupling conditions. Tertiary amides (**1g**) were unreactive under these conditions, only giving back starting material.

Table 1: Trisubstituted Enamides

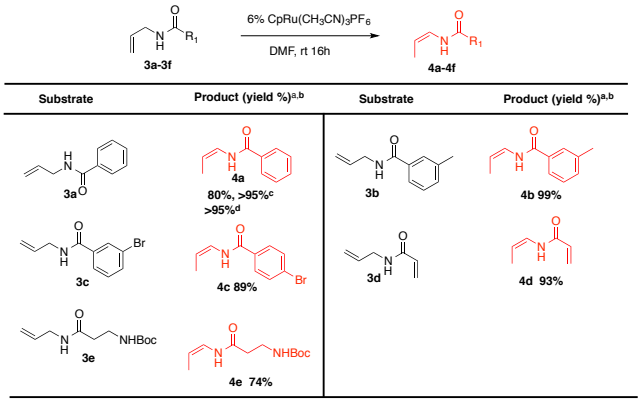


[a]Olefin Selectivity >20:1 by NMR. NOE effects were used to assign geometry
[b]Yields are of isolated material. [c]12% Ru

We next examined whether monosubstituted terminal N-allyl amides could be selectively isomerized under the same conditions (Table 2). Gratifyingly they also reacted with exceptional geometric selectivity to give the thermodynamically less stable Z-enamides in excellent yields. In these cases very minor peaks that may be attributed to the minor trans isomer were visible, however the Z:E ratio in these instances was still exceptional (>20:1). Additionally, when the reaction was run in d_7-DMF, it clearly showed that the selectivity for the conversion of **3a** to **4a** was always excellent (>20:1), and that chromatography was not leading to any enrichment of the Z:E ratio that could account for the excellent selectivities after purification (See SI for Spectra). Subsequent optimization showed that for this olefin substitution pattern, conversion of **3a** to **4a** was >95% complete after 3h using only 3% catalyst.

Z-propenyl enamides have been utilized as excellent substrates for a number of reported asymmetric reactions,[7,24a] however there synthesis remains difficult. There is a single report of using Cu catalysis for the coupling of Z-propenyl bromide with amides but requires 24h at 100 ºC and gives only moderate yields.[25] The base mediated isomerization of allyl benzamide (**3a**) has been reported to give a 1:1 mixture of E:Z isomers.[24b] The alternative hydroamidation of terminal alkynes for the synthesis of Z-enamides has not been applied to propenyl systems.[11]

Table 2: Disubstituted Propenyl Enamides



[a]Olefin Selectivity >20:1 by NMR. NOE effects were used to assign geometry
[b]Yields are of isolated material. [c]6% catalyst NMR conversion after 1h,
[d]3% catalyst NMR conversion after 3h

When we examined the isomerization of terminal allyl Boc-amine **3g** we found that it gave a lower conversion (70 %), and surprisingly gave a modest selectivity for the E isomer (5:1 E:Z) (Figure 3). Interested in finding an alternative amide group that may serve as an easily cleavable protecting group, we next examined formamide **3h**. Gratifyingly isomerization of **3h** gave enamide **4h** in excellent yield and with ~19:1 (Z:E) geometric selectivity. The formamide group is a useful amine protecting group, as well as a stable precursor to isocyanates and formamidines.[26] Vinyl-formamides are an important subunit in a number of bioactive natural products (Figure 3).

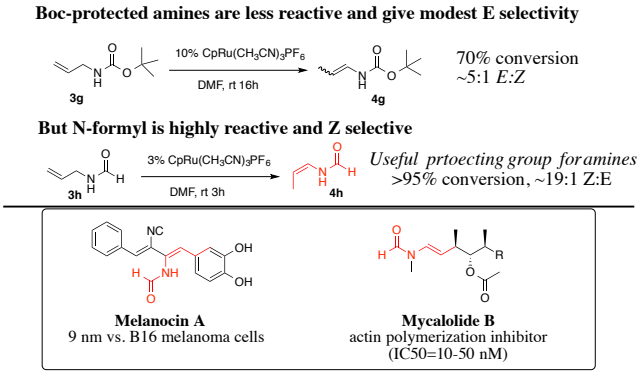
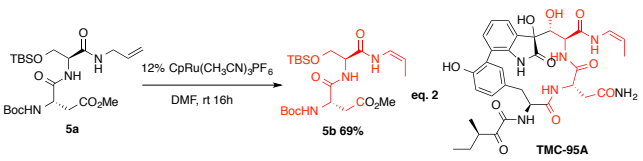


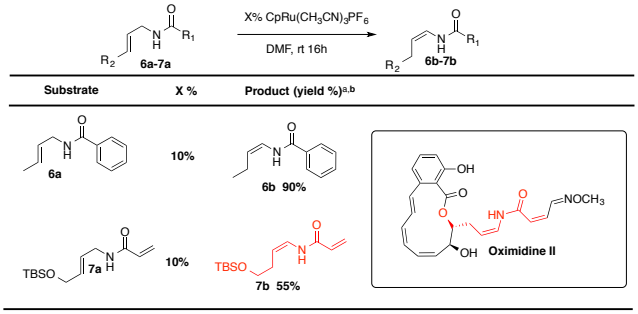
Figure 3: Formamide Directing Groups

In order to further display the utility of this process and highlight its functional group tolerance, we synthesized dipeptide **5a** containing the functional motif seen in TMC-95A (Figure 1)(eq. 2).[8] Gratifyingly after isomerization we isolated enamide **5b** in excellent yield as a single olefin isomer.



For the synthesis of non-propenyl Z-enamides we next examined whether 1,2 disubstituted N-allyl amides were effective substrates (Table 3). The isomerization of amides **6a** and **6b** gave enamides **6b** and **7b** with excellent Z-selectivity (>20:1). Additionally, enamide **7b** was formed with excellent regioselectivity, as no isomerization towards the silyl ether was detected. A number of Z-enamide natural products contain a hydroxyl group in the same spatial orientation (Figure 1), and this is highlighted for natural the natural product oximidine II (Table 3). The isomerization of **6a** and **7a** represent the first reports of a metal catalyzed isomerization of non-propenyl 1,2-disubstituted N-allyl amides towards Z-enamides with excellent geometric selectivity.

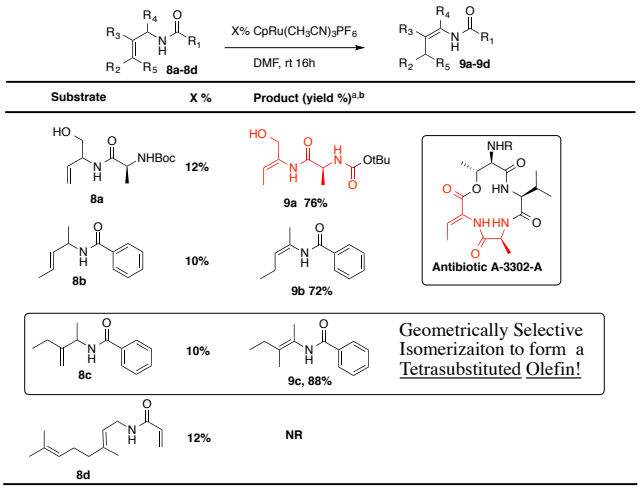
Table 3: Disubstituted Non-Propenyl Enamides



[a]Olefin Selectivity >20:1 by NMR.. NOE effects were used to assign geometry
[b]Yields are of isolated material.

Next, we examined whether branching at the allyl position was tolerated (Table 4). The branched N-allyl amide **8a** isomerized to the stereodefined enamide **9a** in excellent yield and as a single isomer. No protection of the resultant allylic alcohol was necessary, and no additional isomerization towards the free alcohol to form an aldehyde was observed. Alanine was chosen as the amide group, as similar enamide motifs are present in a number of natural products including the antibiotic A-3302-A (Table 4).[27] This result illustrated that substitution at all three positions of the allyl are tolerated. Therefore we next attempted the isomerization of amides **8b** and **8c** (Table 4), which simultaneously contained branching and an additional olefin substitution.

Table 4: Additional Substitution Patterns



[a]Olefin Selectivity >20:1 by NMR. NOE effects were used to assign geometry
[b]Yields are of isolated material.

Enamides **9b** and **9c** were both formed with excellent geometric selectivity (>20:1) and in high yield. Product **9c** represents the first example of forming a geometrically defined tetrasubstituted enamide through an isomerization process. The synthesis of the analogues geometrically defined vinyl halide or triflate necessary for cross coupling would be especially daunting.[28] To the best of our knowledge this isomerization also represents the first example of any olefin isomerization to form an acyclic tetrasubstituted olefin in a geometrically defined fashion. β,β-disubstituted N-allyl amides (**8d**) were unreactive under these reaction conditions.

Allyl boron compounds have been extensively studied as reagents in organic synthesis. They readily undergo stereospecific allylations of aldehdyes,[29] and can be utilized as coupling partners in various C-C bond forming reactions.[30] Thus, we became interested in exploring whether substrates bearing terminal alkenyl boronates could be isomerized effectively and with excellent geometric selectivity. We envisioned rapid access to the necessary staring materials by hydroboration and diborylation of propargyl amides (Figure 4). This, in addition, to the already demonstrated β-borylation[31] to give **1d** and **1e**, would provide all three vinyl boronate starting materials in a single step from commercial or easily prepared starting materials.

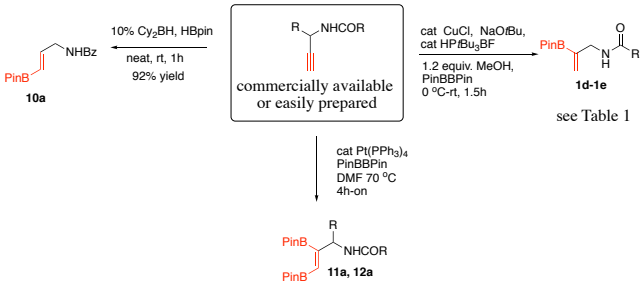


Figure 4: Vinyl Boronates Substrate Synthesis

Gratifyingly, we found that the starting vinyl boronate **10a** could be synthesized in near quantitate yield by the reaction of propargyl amide with neat pinacol borane and catalytic dicylohexylborane.[32] We were especially pleased to find that no protection of the free N-H was required, suggesting that transmetalation of Cy_2BNR_2 with HBpin is facile.

However, our initial attempts to isomerize **10a** proved difficult. The problem appeared to arise from the instability of the product, and crude NMR spectra after aqueous extraction suggested protodeborylation might be the culprit. Surprisingly when we monitored the isomerization reaction by NMR, the process was almost complete within 1h to give enamide **10b**. However there was ~10% of enamide **4a** from protodeborylation (Figure 5). NOE experiments of the crude solution indicated that the only isomer formed was the Z-enamide **10b**. Next we examined the isomerization of N-allyl amide **11a**, and once again, the reaction was complete within 1h to give a single isomer (Figure 5). In this case no protodeborylation of enamide **11b** was observed. Finally, we examined the isomerization of N-allyl amide **12a** (Figure 5). The reaction was once again complete within 1h, highlighting the exceptional rate enhancement in reactivity afforded by the terminal pinacol ester.[33] However, NMR analysis indicated ~75% protodeborylation after 1h, so we subsequently heated the reaction at 80 ºC for 20 minutes to complete the protodeborylation process, providing tetrasubstituted enamide **12b** in excellent isolated yield and as a single geometrical isomer.

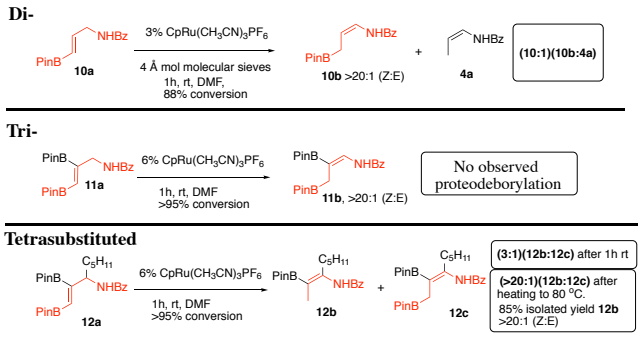


Figure 5: Isomerization of Vinyl Boronates

Although various γ-substituted allyl boronates have been utilized as allylating reagents,[34] there are only 2 reports of synthesizing or using acyclic E-(γ-amidoallyl) boron compounds,[35,36] and no reports of synthesizing the acyclic Z-(γ-amidoallyl) boronate or borane (Figure 6).[37] Thus, we were especially interested in utilizing enamides **10b** and **11b** as allylating reagents. The addition of benzaldehyde to the crude reaction mixture of **10b** in DMF, followed by heating at 70 ºC over 16h gave moderate conversion to amino alcohol **10c** with >20:1 dr. However we were disappointed with the observed protodeborylation of compound **10b** under the standard conditions. Thus, we examined whether less polar solvents were amenable to the isomerization process. We hoped that they would result in less protodeborylation, as well as provide greater reactivity in the allylboration step. Gratifyingly 5 equivalents of DMF relative to substrate in DCM gave a clean isomerization and suppressed protodeborylation to minimal levels, allowing for allylation at a lower temperature and with improved yield (>20:1 dr.) (Figure 6).[38] DMF may act as a ligand to stabilize and turnover the catalyst, since the enamide products likely serve as

good ligands. Next we attempted the addition of aldehyde to the crude solution of trisubstituted enamide **11b** in DMF, followed by heating at 70 ºC over 16h. The reaction gave very clean conversion to give cis amino alcohol **11c** with >20:1 dr.

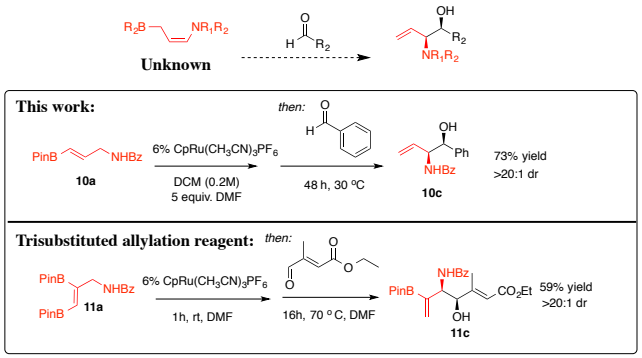


Figure 6: One-Pot Allylation

No protodeborylation of enamide **11b** was observed under the isomerization or allylation conditions. The lower yield is due to the instability of the product **11c** to purification.

HYDROBORATION OF TETRASUBSTITUTED ENAMIDE:

The synthesis of tetrasubstituted acyclic enamides is rare, and therefore there is little information on their reactivity under standard synthetic transformations such as hydroboration. Given that we could easily synthesize tetrasubstituted enamide **9c**, we attempted the hydroboration of **9c** expecting to get the amino alcohol **14a** (Figure 7). The highly polarized nature of enamides has traditionally resulted in excellent selectivity for the β position irrespective of the enamide substituent pattern.[39] However, we were surprised to find that, under traditional hydroboration conditions, we instead formed the product from α addition to give the α-borylamido complex **14b**. Mechanistically the reversal in selectivity may arise from the increased $A^{1,3}$ strain experienced for tetrasubstituted enamides.[40] To minimize strain, rotation of the C_{vinyl}-N bond could lead to intramolecular delivery of borane through coordination with the amide oxygen becoming faster than intermolecular addition of the borane to the tetrasubstituted enamide.

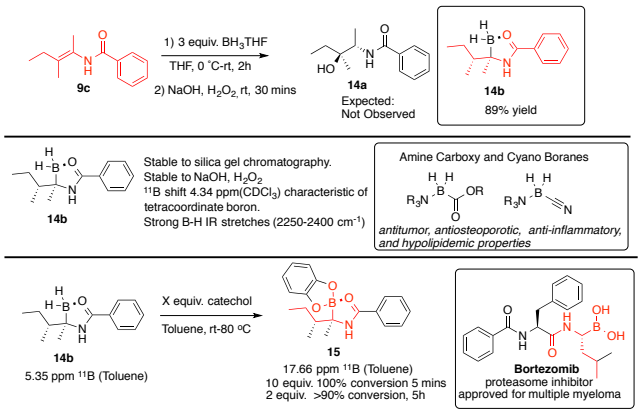


Figure 7: Hydroboration of tetrasubstituted enamide to form α-borylamido complex

There are few examples of non-metal catalyzed heteroatom directed hydroborations using BR_2H regents.[41-42] Therefore, the exceptional selectivity observed for the hydroboration of **9c** with BH_3 as compared to all other examples with enamides, is noteworthy. Further studies will hopefully elucidate additional mechanistic details and may lead to a general α-selective hydroboration of enamides resulting in highly valuable α-boryl amido complexes.

The amidoborane product (**14b**) exhibited unusual stability, which likely arises from chelation of the amide group to form a stable tetravalent borane.[43-44] Analogous tetravalent amino carboxy and cyano boranes have been extensively investigated as isoelectronic analogs of protonated amino acids. They show diverse biological properties, including antitumor, antiosteoporotic, anti-inflammatory, and hypolipidemic activities.[45] However, examples of hydrolytically stable amide chelated boranes have been largely unexplored. Given the increasing interest in α-borylamides[46] we attempted to convert the borane **14b** into a boronate ester. Amidoborane **14b** was easily converted to the catechol ester **15** by heating in the presence of excess catechol in toluene (Figure 7). The α-borylamide motif has been shown to interact with serine residues to form tetravalent boronates that mimic the transition state structures observed during proteasome activity. The α-boryldipeptide bortezomib was the first proteasome inhibitor to be tested in humans and is marketed for use against multiple myeloma and mantle cell lymphoma. Synthetically, α-borylamides also display differential, and oftentimes enhanced, reactivity for metal catalyzed cross coupling reactions.[47]

MECHANISTIC PROPOSAL:

The conserved spatial orientation of the original olefin and amide across all substrates examined suggests an isomerization mechanism involving a chelation controlled C-H activation. When we added 1 catalyst equivalent of PPh_3 to our standard conditions we obtained a ~1:1 E:Z mixture of enamide isomers for the isomerization of allyl benzamide **3a**. Additionally work by Grotjahn using a hemilabile bidentate ligand is reported to give the E isomer as the only product.[18b] This suggests the selectivity in our case requires *three* open coordination sites on the CpRu catalyst. The precatalyst $CpRu(CH_3CN)_3PF_6$ rapidly loses the acetonitrile ligands upon solvation and readily forms complexes with alkenes.[22] Simultaneous coordination of the amide and olefin to the highly unsaturated Ru catalyst (**I**) followed by C-H abstraction to give intermediate **II** is likely the product-determining step (Figure 8). Reductive elimination forms enamide **III** and subsequent ligand exchange with additional N-allyl amide **V** gives the desired enamide **IV**.

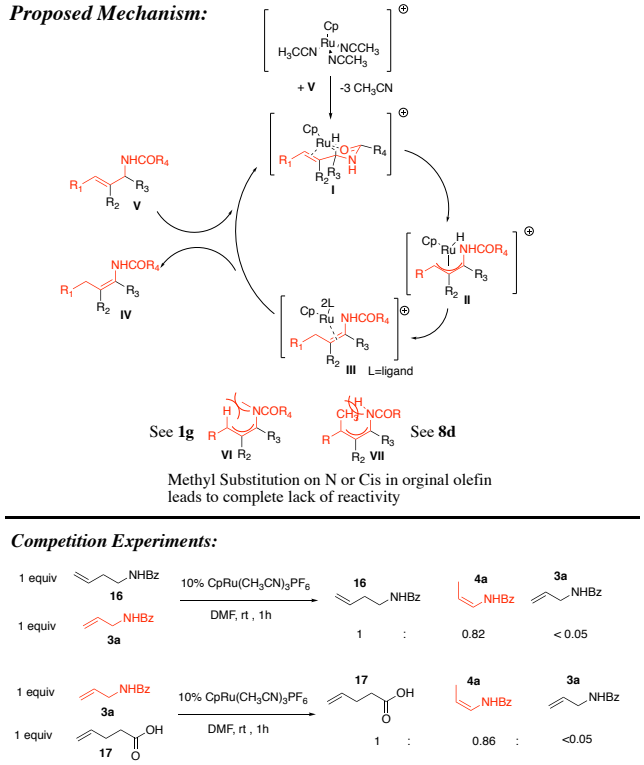


Figure 8: Mechanistic Proposal

When methyl is substituted for the N-H (**VI**)(see **1g**, Table 1), or cis to the N-allyl amide (**VII**)(see **8d**, Table 4) the reaction produces no product. This supports the proposed mechanism, since both substitutions would lead to additional $A^{1,3}$-strain in the proposed π-allyl intermediate. The importance of *both* coordination of the amide and double activation of the C-H (allylic and α to the amide) is supported by competition experiments between allyl benzamide **3a** and either **16** or **17**. Terminal alkenes **16** and **17** both contain chelating groups which could provide access to chelate structures similar to proposed intermediate **I**, however, do not contain a doubly activated C-H**.** In both cases conversion of N-allyl amide **3a** to enamide **4a** was complete within an hour, while both **16** and **17** remained almost completely unreacted. Finally, the lack of reactivity associated with allyl silyl ethers, which also contain a doubly activated C-H, but not the same chelating ability, again supports the requirement for *both* chelate structure **I** and a doubly activated C-H.

Interestingly, the enamide geometry observed from the alkene-alkyne coupling (**B**) (Figure 9), compared to that obtained through the isomerization process (**C**), supports the assertion that in the case of the alkene-alkyne coupling a ruthenacyclopentene intermediate is operative.[23] An alternative mechanism involving a C-H activation to give intermediate **I**, followed by carbometalation **II**, and reductive elimination, would be expected to give product **D**, which has never been observed. This suggests that when an alkyne is present, the observed products **B** and **C** arise from two different mechanistic pathways.

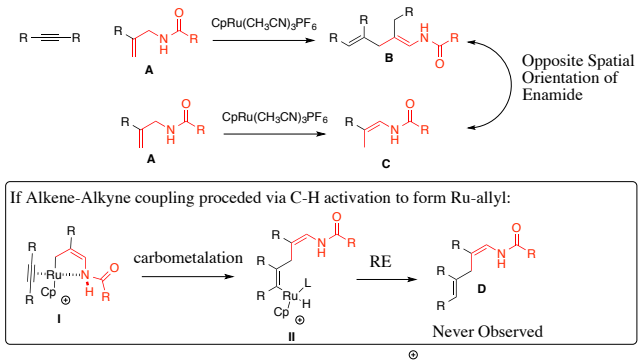


Figure 9: Additional Mechanistic Consideration

CONCLUSION:

In summary, we have reported a general method for the synthesis of geometrically defined di-, tri-, and tetrasubstituted enamides. The starting olefin substation pattern determines the resultant enamide geometry. The breadth of starting olefin substitution patterns that are reactive, including 1,1-disubstituted (Table 1), monosubstituted (Table 2), 1,2-disubstituted (Table 3), branching (Table 4), 1,1,2-trisubstituted (Figure 5), and 1,1,2-trisubstitued with branching (Figure 5), is remarkable. The reactivity and geometric selectivity that is observed likely arises from the role of chelation in the mechanism to both control the geometry and improve the reactivity. In this regard the highly unsaturated precatalyst $CpRu(CH_3CN)_3PF_6$ was found to be differential. The method displays exceptional chemoselectivity, as demonstrated by the large number of functional groups that are compatible, including aryl halides, free alcohols, and boronic esters. These functionalities would be difficult to incorporate using Cu catalyzed cross couplings towards enamides. Additionally, other alkene functionalities (Figure 8, **16** and **17**)(**3d**, Table 2), which could pose difficulties for other metal catalyzed isomerizations, are tolerated. The isomerization of vinyl boronates **(10a** and **11a,** Figure 6) provides rapid access to Z-enamide allylating regents for forming *cis* vicinal amino alcohols. Additionally, an unusual regioselectivity for hydroboration of enamides has been observed, and represents a novel route to α-borylamides. We believe this method should provide a complementary approach to Cu and Pd catalyzed C-N couplings towards geometrically defined enamides and provides the desired products with much greater atom economy.

ASSOCIATED CONTENT

Supporting Information. Experimental details, compound characterization data, and spectra. This material is available free of charge via http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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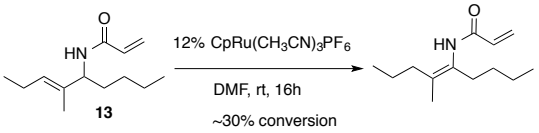

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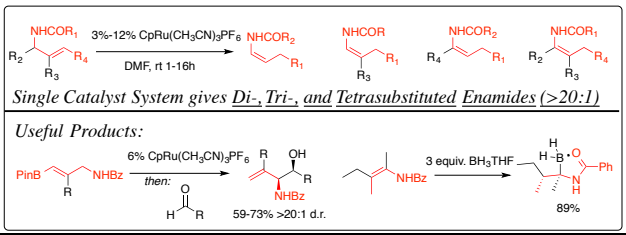
NHCOR1
R2
R4
R3
3%-12% CpRu(CH3CN)3PF6
DMF, rt 1-16h
NHCOR2
R1
NHCOR
NHCOR2
NHCOR1
Single Catalyst System gives Di-, Tri-, and Tetrasubstituted Enamides (>20:1)
Useful Products:
PinB
NHBz
6% CpRu(CH3CN)3PF6
then:
OH
59-73% >20:1 d.r.
3 equiv. BH3THF
89%
Ph

9