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COMMUNICATION

Highly Diastereo- and Branched-Selective Rearrangement of Substituted *N*-Alloc-*N*-Allyl Ynamides

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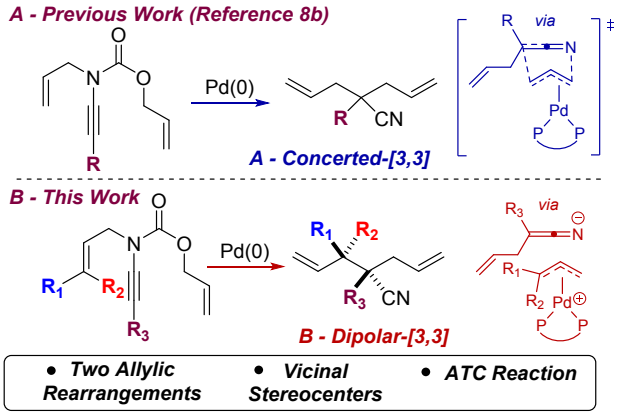
An auto-tandem catalytic, branched-selective rearrangement of substituted *N*-alloc-*N*-allyl ynamides was developed. This reaction provides ready access to complex quaternary nitrile products with vinylogous stereocenters in excellent diastereoselectivity, including contiguous all-carbon quaternary centers. The stereochemical outcome is determined via a Pd(0) catalyzed dipolar ketenimine aza-Claisen rearrangement and computational studies exemplify the key role ligand geometry plays.

Using a single catalyst to perform multiple, mechanistically distinct reactions (auto-tandem catalysis [ATC])[1] can be a very powerful approach in synthesis.[2] ATC reactions are particularly impactful when multiple C-C bonds are formed,[3] especially if stereogenic elements are generated during these processes. Of particular interest is the formation of all-carbon quaternary centres using ATC approaches.[4]

The high reactivity and linear geometry of unstabilized nitrile anions have made them problematic in many catalytic reactions. Lewis basic additives (to form aggregated complexes),[5] decarboxylative/deacylative approaches,[6] and silyl ketenimines[7] have all been utilized, however many challenges remain. Our contribution to the field was developing a Pd-catalysed rearrangement of *N*-alloc-*N*-allyl ynamides which formed quaternary diallyl nitriles (Scheme 1A).[8,9] This ATC process performs two mechanistically distinct allylic rearrangements and avoids requirement for nitrile anion intermediates. During this study we discovered that Pd(0) was acting as a nucleophilic catalyst, donating electron density into the $\sigma^*_{C\text{-}N}$ orbital triggering a concerted [3,3]-rearrangement (Scheme 1A). In contrast, other Pd-catalysed aza-Claisen rearrangements proceed through a π-Lewis acidic Pd(II) pathway.[10] We reasoned that substrates encompassing γ-substituted *N*-allyl groups would provide branched products containing two contiguous stereogenic centers in this reaction.

Scheme 1: ATC Rearrangement of *N*-Alloc-*N*-Allyl Ynamides.



Moreover, if substrates include γ,γ-disubstitution, contiguous all-carbon quaternary stereocenters could be formed. Importantly, these are mechanistically distinct from previously disclosed branched-selective allylations.[11] Herein, we report the development of a highly diastereoselective ATC reaction with complete branched selectivity under very mild conditions (Scheme 1). Of particular note is the dipolar allyl ketenimine-[3,3]-rearrangement which achieves high levels of diastereoselectivity, including the formation of vicinal all-carbon quaternary stereocenters (Scheme 1B).

Optimization studies revealed that a variety of bidentate phosphine ligands provided complete branched selectivity (**2a**). Of note, were catalytic systems derived from Pd_2dba_3 and phosphine ligands (**L1-3**) due to the abundance of commercially available variants (Table 1). Unsubstituted phenyl, alkyl and furyl substituted ligands (**L1a-c**) gave poor reactivity and selectivity (Entries 1-3). Ligands containing 3,5-disubstituted phenyl groups (**L1d-e**) led to improved selectivity (Entries 4 & 5). The addition of electron donating groups at the 4-position (**L1f-h**), improved both yield and selectivity (Entries 6-8), with DTBM-MeOBiphep (**L1g**) proving optimal. Other DTBM substituted ligands (**L2g** /**3Lg**, Entries 9 & 10) also provided selectivity, but with poor reactivity.

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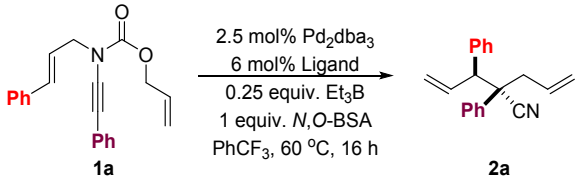
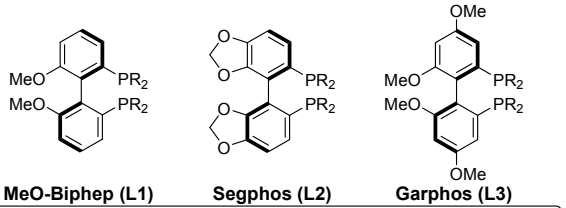
[b] *Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x*

Table 1: Selected Optimization Studies[a]



Entry	Ligand	Yield[b]	d.r.[d]
1	(*R*)-MeOBiphep (**L1a**)	11%	1.8:1
2	(*R*)-i-Pr-MeOBiphep (**L1b**)	5%	1:1.2
3	(*R*)-Fur-MeOBiphep (**L1c**)	35%	1:1.1
4	(*R*)-DM-MeOBiphep (**L1d**)	8%	3.6:1
5	(*R*)-DTB-MeOBiphep (**L1e**)	20%	5.4:1
6	(*R*)-DMM- MeOBiphep (**L1f**)	40%	9:1
7	(*R*)-DTBM-MeOBiphep (**L1g**)	70% (63%)[c]	13:1
8	(*R*)-*i*Pr-Me$_2$N-MeOBiphep (**L1h**)	57%	13:1
9	(*R*)-DTBM-Segphos (**L2g**)	15%	13:1
10	(*R*)-DTBM-Garphos (**L3g**)	25%	5:1



MeO-Biphep (L1) **Segphos (L2)** **Garphos (L3)**

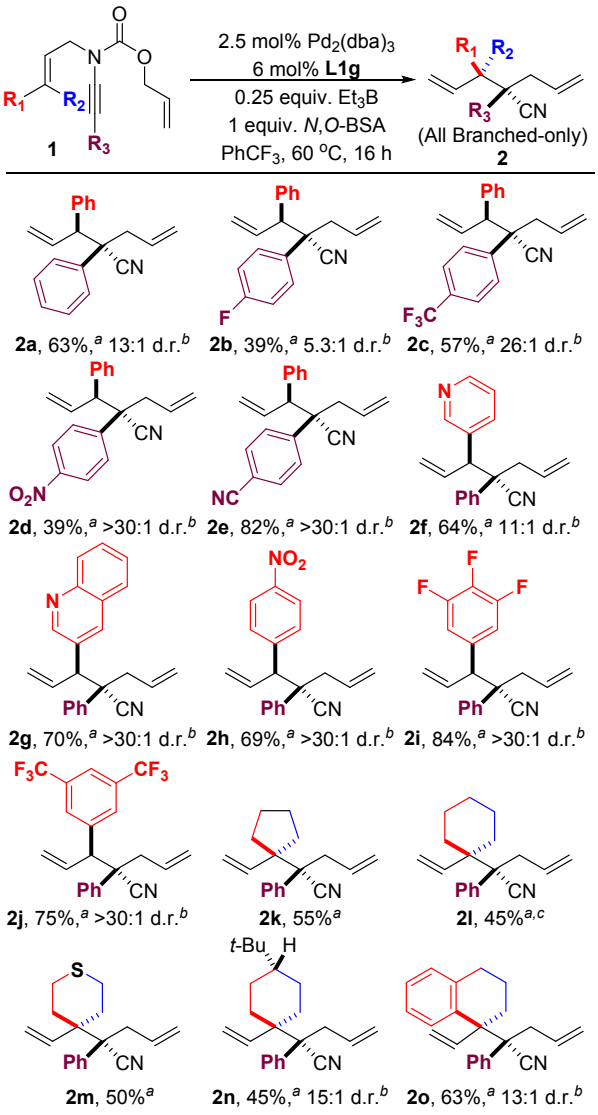
R = Ph (**a**); *i*-Pr (**b**); 2-Fur (**c**); 3,5-Me-Ph (**d**); 3,5-*t*-Bu-Ph (**e**); 3,5-Me-4-MeO-Ph (**f**); 3,5-*t*-Bu-4-MeO-Ph (**g**); 3,5-*i*-Pr-4-Me$_2$N-Ph (**h**)

[a] For detailed optimization studies, see SI; [b] Determined by ^{1}H NMR using mesitylene as internal standard; [c] Isolated yield; [d] Determined by ^{1}H NMR of crude.

With the optimized conditions in hand (Table 1, Entry 8), we began examining the substrate scope (Scheme 2). Substitution on the ynamide phenyl group was investigated and the stereochemical outcome appears to be influenced by the mesomeric stabilization of an anion,[12] suggesting a dipolar mechanism (Scheme 1B). Weakly π-donating groups, such as fluorine (**1b**, σ-=-0.03), gave lower selectivity than **1a**, whereas strongly anion stabilizing groups including CF_3 (**1c**, σ-=0.65), NO_2 (**1d** σ-=1.27), and CN (**1e**, σ-=1.00) provided very high levels of stereoselectivity (≥26:1 d.r.). Next our attention turned to modulation of the γ-substituted N-allyl group. Basic heterocycles could be tolerated in this reaction with pyridine (**1f**) and quinoline (**1g**) variants providing high yields and diastereocontrol. Other substitution could be tolerated on the migrating allylic group, with electron deficient groups providing excellent outcomes. 4-Nitro (**1h**), 3,4,5-trifluoro (**1i**), and 3,5-bis-(trifluoromethyl) (**1j**) substrates all gave high chemical yields with exquisite diastereoselectivity.

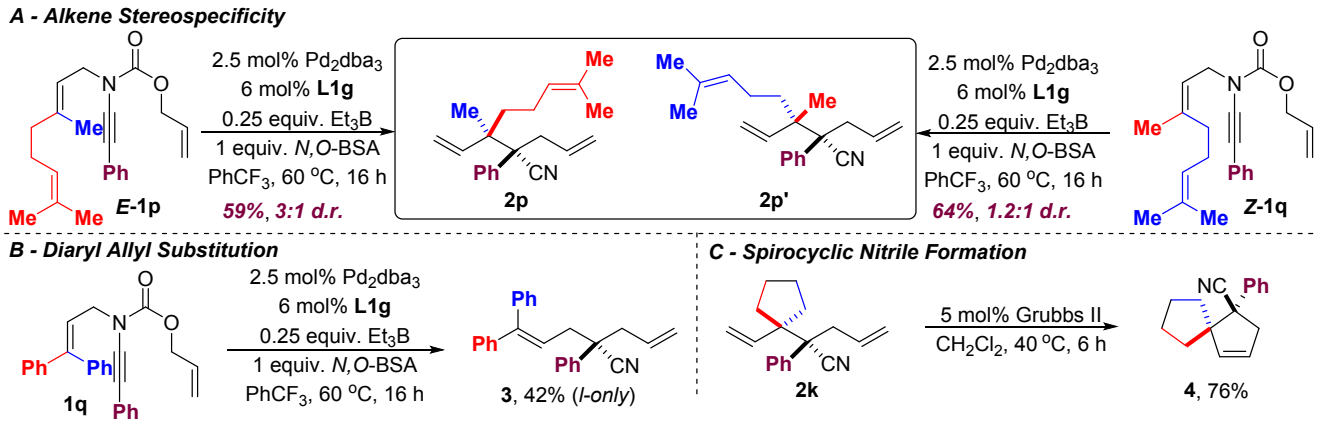
γ,γ-Disubstituted *N*-allyl groups were also examined, which upon rearrangement, produced highly congested vicinal all-carbon quaternary centers. Cycloalkyl and thiopyranyl substituted ynamides (**1k-m**) variants gave highly efficient routes to cyclic branched nitriles **2k-m**. We also investigated diastereoselectivity in the formation of contiguous all-carbon quaternary centers. Facial selectivity on the *N*-allyl group was probed by installing a 4-*tert*-butyl cyclohexyl group (**1n**), which provided the **2n** in 15:1 d.r. The formation of two contiguous all-carbon stereogenic centers could also be achieved, with tetralone derived ynamide **1o** providing nitrile **2o** in good yield and an impressive 13:1 d.r. This example (**1o** to **2o**) demonstrates the power of this approach in forming very congested C-C bonds as part of an auto-tandem catalytic sequence with high-levels of diastereoselectivity.

Scheme 2: Substrate Scope



[a] Isolated yield; [b] Determined by ^{1}H NMR; [c] **2l** produced in 16% ee.

The stereospecificity of this reaction was further investigated by comparing the relative outcomes using *E* and *Z*-carbamates ***E*-1p** and ***Z*-1p** (Scheme 3A). Both reactions proceeded with similar chemical efficiency, however ***E*-1p** provided a 3:1 mixture of diastereomers (**2p**:**2p'**), whereas the ***Z*-1p** resulted in a 1.2:1 ratio. These outcomes demonstrate stereospecificity, albeit with a competing isomerization pathway. This π-σ-π pathway is a common source of low stereoselectivity with acyclic *Z*-π-allyl donors.[13] Interestingly, γ,γ-diphenyl substituted allyl ynamide **1q** provided the only example where linear selectivity was achieved, affording nitrile **3** as a single isomer (Scheme 3B). This alternative regiochemistry can be rationalized due to the



Scheme 3: Additional Allylic Substitution and Synthetic Utility Studies.

increased conjugation of the linear isomer and the additional steric encumbrance in the branched product. Indeed, only one example of branched selectivity from a 1,1-diphenyl π-allyl metal species has been reported.[14] The cyclic products could be converted in to spirocycles using Grubb's 2nd generation catalyst to form [5,5]-spirocycle **4** in excellent yield (Scheme 3C).

To elucidate the origin of diastereoselectivity, we conducted a DFT study of the formation of **2a** at CPCM(Trifluorotoluene) M06L/BSII//ONIOM(M06L/BSI:PM6) level of theory (for BSI and BSII see Scheme 4 footnote). We found the palladium bound ligand (**L1g**) forms a deep cleft in which reactivity occurs. This conformational restriction results in a dissociative formal process rather than a concerted [3,3]-rearrangement.[8b] Although ketenimines are stereogenic, they are highly epimerizable and exist as a dynamic mixture of isomers.[16] Allyl ketenimine **6** coordinates deep within the binding pocket, forming diastereomeric complexes **7**/**13**. These interconvertible complexes (**7**/**13**) ionize though transition states **TS-8**/**TS-14**, determining the stereochemistry and forming ion pairs **9**/**15**. A possible explanation for this selectivity is the coplanarity of the phenyl groups leading to an offset π-stacking interaction (3.5 Å) in **TS-8** that is not present in **TS-14**.[17] Indeed, an IGM 3D plot showed an isosurface consistent with a non-covalent stabilizing interaction between the two aromatic rings in **TS-8** (see SI for full details).[18] The possibility of competing concerted [3,3]-process was considered;[8b] however, **7**/**13** do not have the necessary orbital overlap and no [3,3]-transition state could be located. The dihedral angle between the allylic termini and the phosphines can be used to highlight the conformational changes required between C-N bond breaking and C-C bond formation. Following ionization, the two reaction pathways diverge for C-C bond formation. In the major pathway, ion-pair **9** (5.9°) undergoes a reorganization of the ligand, rotating the π-allyl group within the cleft. Initially, intermediate **10** (12.3°) is formed, which is in reactive conformation for C-C formation *via* **TS-11** (-13.9°; +1.0 kcal/mol from **10**), to afford **12**. In contrast, ion pair **15** (21.6°) is much further from the reactive conformation for C-C bond formation, requiring rotation through **TS-16** (0.7°; +1.4 kcals/mol from **15**). This produces shallow intermediate **17** (-13.1°) before proceeding directly into a C-C bond formation *via* **TS-18** (-14.2°, 0.1 kcal/mol), to form nitrile **19**. Despite the dipolar pathway, the ion pair does not fully dissociate or solvent separate, with the energetics suggesting a very rapid C-C bond formation following ionization.

In conclusion, a highly diastereoselective ATC method for the construction of stereochemically complex nitriles has been developed. This provides a highly attractive route to nitriles containing an all-carbon quaternary stereocenter and further vicinal substitution, including contiguous all-carbon quaternary stereocentres. In addition, we have developed a highly accurate computational model to deconvolution of the ketenimine rearrangement mechanism, including the discovery of a dipolar [3,3]-process which occurs in a deep cleft within the catalyst.

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Conflicts of interest

There are no conflicts to declare.

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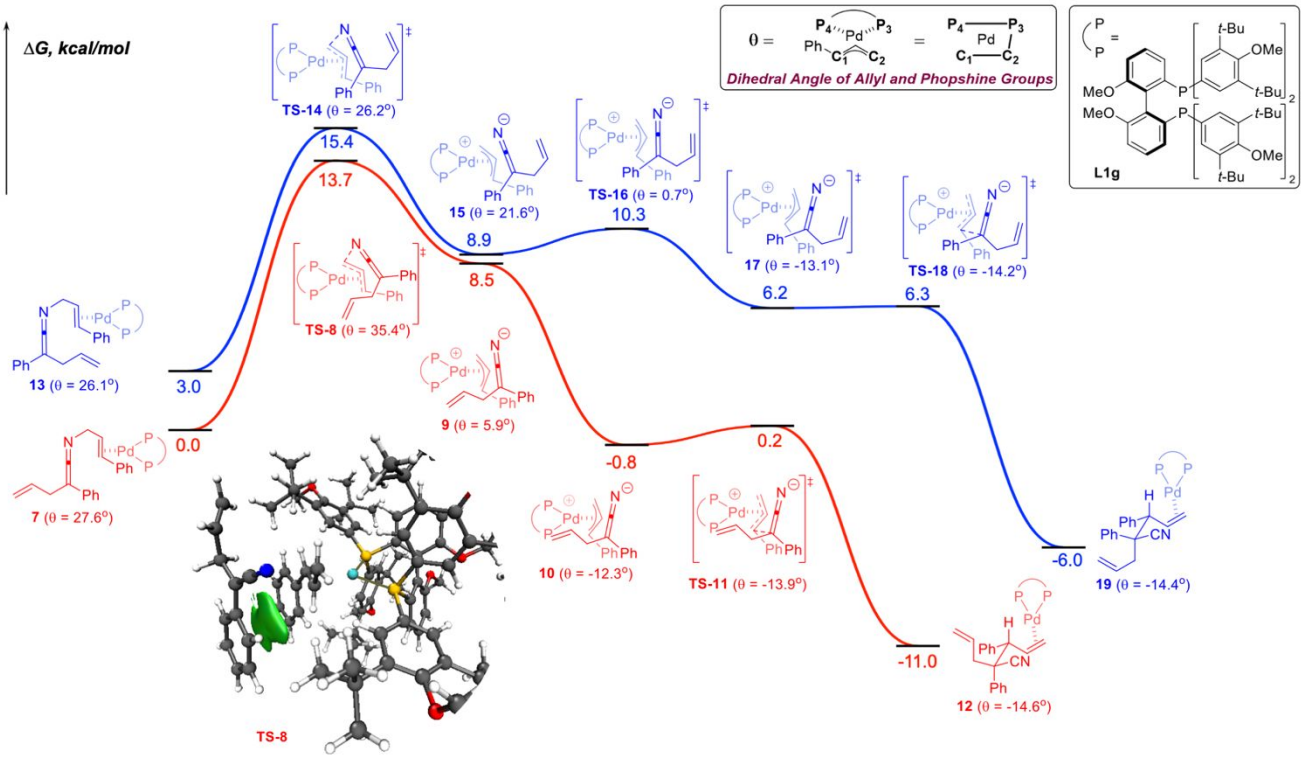

Scheme 4. Summary of DFT Analysis Examining the Diastereoselectivity in the Formation of **2a**. [a] DFT calculations done at CPCM(Trifluorotoluene) M06L/BSII//ONIOM(M06L/BSI:PM6), where BSI = 6-31+G(d) (C, H, P, O)/LANL2DZ (ECP Pd) and BSII = 6-311++G(2d,2p) (C, H, P, O) /LANL2DZ (ECP Pd); [b] Quasi-harmonic solvent and temperature (333.15 K) corrected Gibbs free energies at 1 mol/L standard state are reported; [c] For optimized structures, see SI.

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