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Palladium-Catalyzed, Enantioselective Formal Cycloaddition between Benzyltriflamides and Allenes: Straightforward Access to Enantioenriched Isoquinolines

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Supporting Information

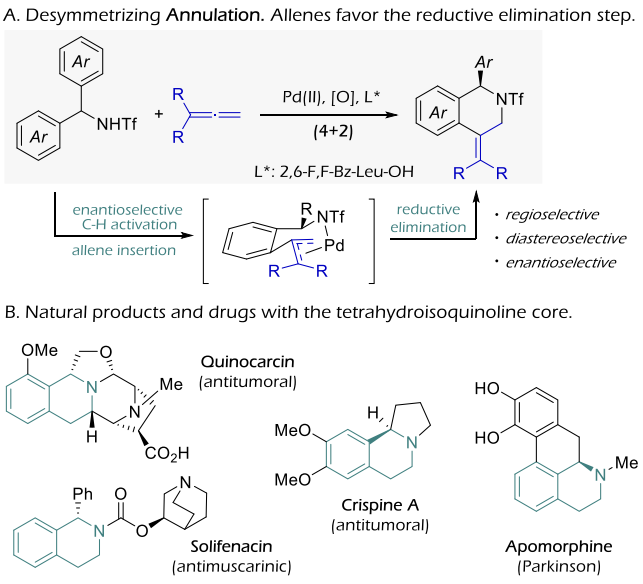
ABSTRACT: Benzyl and allyltriflamides can engage in Pd-catalyzed oxidative (4+2) annulations with allenes, to produce highly valuable tetrahydroisoquinoline or dihydropyridine skeletons. The reaction is especially efficient when carried out in the presence of designed N-protected amino acids as metal ligands. More importantly, using this type of chiral ligands, it is possible to perform desymmetrizing, annulative C−H activations of prochiral diarylmethylphenyl amides, and thus obtain the corresponding isoquinolines with high enantiomeric ratios.

The metal-catalyzed functionalization of nonactivated C−H bonds has emerged as an extremely powerful synthetic tool.[1] Moreover, if the C−H activation is appropriately harnessed to encompass a concomitant annulation reaction, the methodology allows a direct assembly of cyclic skeletons from simple, nonfunctionalized acyclic starting materials.[2] In this context, we have reported several Rh and Pd-catalyzed annulations of alkenylphenols and alkenylanilides with different unsaturated partners. These strategies allow to build a variety of heterocyclic products in a straightforward manner.[3] The use of allenes as annulation partners is particularly attractive owing to their inherent reactivity, and because they favor reductive elimination versus β-hydride elimination steps in key metallacyclic intermediates.[4]

Owing to this special reactivity, we wondered if allenes could engage in annulative C−H functionalizations of benzyl- or allylamines, as this would allow to build highly valuable tetrahydroisoquinoline and tetrahydropyridine skeletons from simple precursors. Achieving these transformations is far from obvious, not only because of the difficulties associated with the C−H activation and allene insertion steps but also because of competing benzylic or allylic oxidation reactions. Indeed, the only precedent in this type of annulations involves the use of α,α-disubstituted benzylamines (which cańt be oxidized) and monosubstituted allenes, and provides mixtures of isomeric adducts.[5,6]

Herein, we report the discovery of conditions that allow to carry out efficient Pd-catalyzed annulations between benzylamides and allenes. The reaction works for α-unsubstituted and monosubstituted benzyltriflamides, and different types of allene partners, and takes place with excellent regio- and stereoselectivities. The annulation can be extended to allyl and even homoallylamines, thereby allowing to build dihydropyridine and azepine skeletons. More importantly, we demonstrate that the tetrahydroisoquinoline products can be assembled in an efficient and highly enantioselective manner via desymmetrization of prochiral starting materials (Scheme 1A). While several desymmetrizing C−H activation/functionalization processes have been described, especially under Pd-catalysis,[7−9] to the best of our knowledge, palladium-catalyzed enantioselective formal cycloadditions relying on C−H activations are unknown.[10] Moreover, the number of reports on any desymmetrizing metal-mediated annulations involving C−H activations is marginal.[11]

Scheme 1. Asymmetric C−H Activation/Annulation Approach to Isoquinoline Skeletons



Finally, it is important to note that tetrahydroisoquinoline skeletons are privileged scaffolds present in a vast amount of bioactive natural products and drugs (Scheme 1B), and therefore the development of enantioselective approaches to these cyclic skeletons is of major significance.[12]

Considering our previous work on the annulation of alkenylanilides and allenes under palladium catalysis,[3e] we

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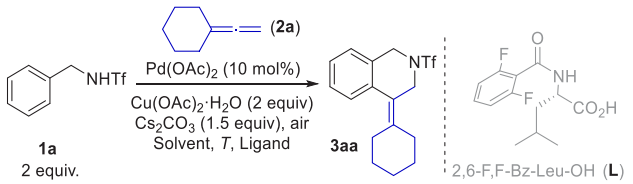
began our research by exploring the reaction between benzyltriflamide **1a** and vinylidenecyclohexane (**2a**) in the presence of 1.5 equiv of Cs_2CO_3, and using Pd $(OAc)_2$ as catalyst, and $Cu(OAc)_2$ as reoxidant. With *tert*-amyl alcohol as solvent, the desired (4+2) cycloadduct was isolated in a modest 15% yield. The use of other solvents, at the same temperature (80 °C), allowed for little improvements (up to 23−25% yield, Table 1, entries 1−5). Although the presence of

Table 1. Optimization of the Reaction Conditions[a]



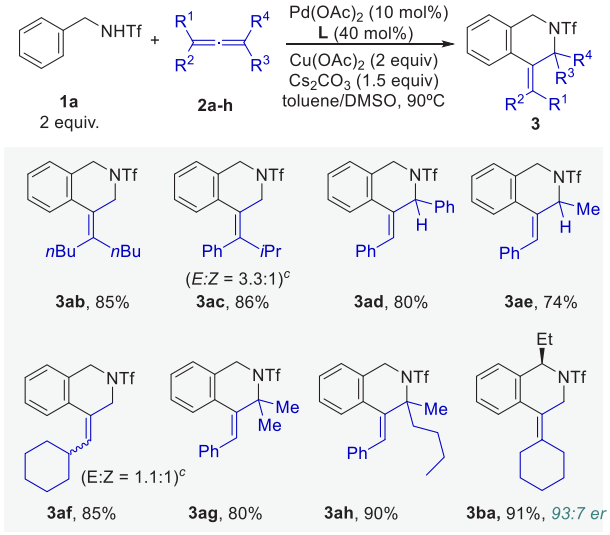
Entry	Solvent	*T*	Ligand[b]	Yield[c]
1	*t*-AmyOH	80 °C	–	15%
2	Dioxane	80 °C	–	23%
3	DCE	80 °C	–	24%
4	CH_3CN	80 °C	–	9%
5	Toluene	90 °C	–	25%
6[d]	Toluene	90 °C	–	34%
7	Toluene	90 °C	Boc-Leu-NHOMe	37%
8	Toluene	90 °C	Boc-Phe-NHOMe	31%
9	Toluene	90 °C	Boc-Ala-OH	58%
10	Toluene	90 °C	Boc-Val-OH	69%
11	Toluene	90 °C	2,6-F,F-Bz-Leu-OH	85%
12[d]	Toluene	90 °C	2,6-F,F-Bz-Leu-OH	95%[e]
13[d]	Toluene	90 °C	2,6-F,F-Bz-Leu-OH	86%[e,f]

[a]Conditions: 0.333 mmol **1a**, 0.167 mmol of allene **2a**, 2 mL of solvent, under air, 16 h. [b]40% of ligand. [c]Yields based on **2a**, calculated by using an internal standard. [d]15 equiv of DMSO added. [e]Isolated yield based on **2a**. [f]0.5 equiv of $Cu(OAc)_2·H_2O$

the triflyl substituent in the amine slows down the benzylic oxidation, the formation of undesired benzylaldehyde was still significant (observed after the work-up). While the addition of DMSO in toluene allowed a slight increase in the yield to 34%, we found that adding protected amino acids (entries 6−10), and especially 2,6-F,F-Bz-Leu-OH (**L**, 40 mol %), boosts the yield up to 85% (entry 11). This could be further improved by adding 15 equiv of DMSO to the reaction mixture (95% yield, entry 12), with the reaction being complete after only 40 min. The role of the DMSO is unclear, but it may help to stabilize Pd(0) intermediates and favor a more effective reoxidation to Pd(II). Finally, the amount of $Cu(OAc)_2$ can be decreased to 50 mol % without significantly affecting the yield (entry 13).

Using the optimized conditions, we found that the reaction can be extended to different types of allenes (see Table 2). Thus, other 1,1-dibsubstituted allenes like 5-vinylidenenonane (**2b**) or (4-methylpenta-1,2-dien-3-yl)benzene (**2c**) led to the corresponding isoquinolines **3ab** and **3ac** in 85 and 86% yield. 1,3-Disubstituted allenes **2d** and **2e** provided the corresponding adducts **3ad** and **3ae**, as only one stereo- and regioisomer (80 and 74% yield, respectively). Monosubstituted allenes like propa-1,2-dien-1-ylcyclohexane also work, to give **3af** as 1.1:1 mixture of *E*:*Z* isomers. More impressively, trisubstituted allenes led to only one cycloadduct in a very efficient manner (**3ag** and **3ah**, 80 and 90% yield, respectively). It is important to note that diphenylacetylene or styrene failed to react with **1a** under the standard reaction conditions, which supports the

Table 2. Pd(II)-Catalyzed Annulation of N-Benzyltriflimides with Allenes[a]



[a]Isolated yield based on allenes, after 16 h. [b]*E*:*Z* and regioisomeric ratios are >20:1, unless otherwise noted. [c]Inseparable isomers. Regioisomeric ratio determined by crude ^1H NMR.

special reactivity of allenes in this type of palladium catalyzed annulations.

The reaction is not limited to unsubstituted benzyltriflamides, and thereby α-alkyl benzyltriflamides can participate in the annulations, providing for efficient kinetic resolutions. Therefore, treatment of 2 equiv of (1-phenylpropyl)triflamide (**1b**) with allene **2a**, using standard conditions, produced a 91% yield of cycloadduct **3ba** (45% yield based on the triflamide **1b**, Table 2) with a very good 93:7 enantiomeric ratio (er). We also isolated a 40% yield of enantioenriched starting amide (er = 86:14).

Next, we wondered if the annulation could be extended to more challenging triflamides bearing alkenyl instead of benzyl pendants. Palladium-catalyzed activations of olefinic C(sp^2)−H bonds has been much less developed than that of their aromatic counterparts, in part because of competing alkene addition reactions. Gratifyingly, using the above conditions, allene **2a** reacted efficiently with allylamines **1c** and **1d** to produce the expected tetrahydropyridines **3ca** and **3da** in 71 and 88% yield (Table 3).[13] This reaction is general for other allenes as exemplified with trisubstituted derivative **2g** that led to the formation of **3cg** in an excellent 90% yield.

Interestingly, in a rare example of a formal (5+2) annulation, the transformation can be extended to homoallylic amines, as demonstrated with the assembly azepine **3ea** (83%). This preliminary result proposes a trivial and practical entry to seven-membered azaheterocycles, and warrants further future research to explore the scope of the process.

While the above examples demonstrate that using N-triflyl protected amines and allenes it is possible to achieve very appealing annulative C−H activations, the efficiency of the kinetic resolution to give optically active isoquinoline **3ba**, called for exploring asymmetric variants based on desymmetrization strategies. Gratifyingly, treatment of the diphenylmethylamide **1f** with allene **2a**, under standard conditions at 90 °C, gave the expected cycloadduct **3fa** with an excellent 85% yield and a very good 94:6 enantiomeric ratio. Similar results were obtained with other disubstituted allenes such **2b** and **2c**,

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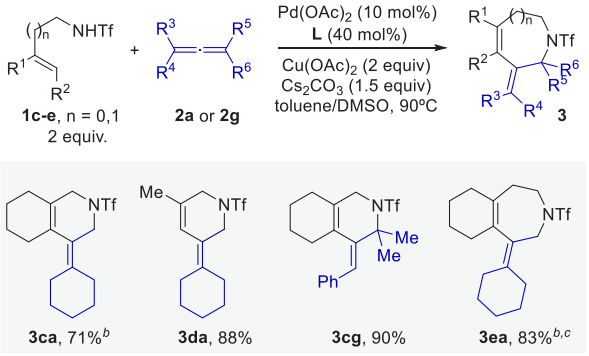
Table 3. Pd(II)-Catalyzed Annulation between N-Allyl (and Homoallyltriflamides) and Allenes[a]



[a]Isolated yields based on allenes **2** after 16 h. [b]105 °C. [c]An equimolar amount of **1e** and **2a** was used.

which gave the products **3fb** and **3fc** with yields between 66 and 95%, and 95:5 er ratios. Remarkably, using a monosubstituted allene (propa-1,2-dien-1-ylcyclohexane, **2f**), we obtained an excellent yield (81%) and er (93:7) of the adduct **3ff** and, contrary to the reaction with the unsubstituted benzyltriflamide (Table 2), we only observed the *Z* isomer.

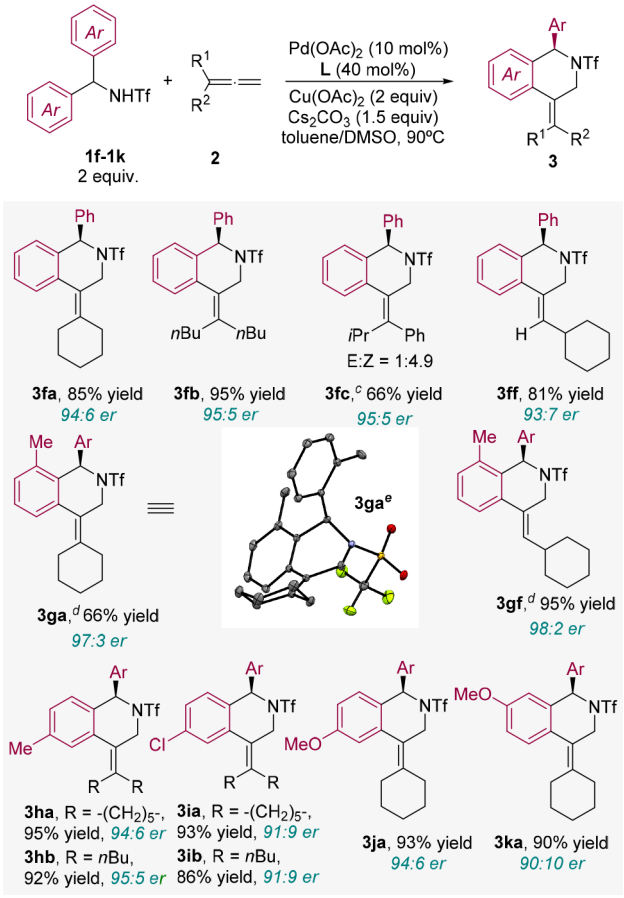
Other prochiral substrates featuring different substituents at the aryl moiety also participated in the annulation. Therefore, products like **3ga** or **3gf**, in which the phenyl groups have *ortho* methyl substituents, were produced in excellent yields and with enantiomeric ratios of 97:3 and 98:2. A crystal structure of **3ga** allowed to stablish the absolute configuration of the chiral center (Table 4). For the case of *para* substituted aromatic rings, the reaction was also very efficient, and products **3ha**, **3hb**, **3ia** and **3ib**, were isolated in yields of 86−95% yields, and enantiomeric ratios of up to 95:5. Finally, cycloadducts with methoxy substituents in *para* or *meta* positions of the aromatic rings were also efficiently formed (**3ja** and **3ka**), although the enantiomeric ratio slightly dropped to 90:10 for the latter.

A hypothetical catalytic cycle depicted in Scheme 2 allows to infer key elements that are critical for the success of the above annulations. The triflyl group should favor deprotonation at the nitrogen, and the formation of intermediates like **I**, in which eliminations of benzylic hydrogens might be not especially easy.[14] The amino acid ligand likely plays a key role in facilitating the C−H activation to give palladacycle **IIb**, which after coordination of the allene would form intermediate **III**. This intermediate evolves by migratory insertion to give a π-allylic palladacycle (**IV**), which undergoes a N−C sp^2 reductive elimination, favored by the presence of the coordinating exoalkene group. Pd(0) is reoxidized to the active Pd(II) catalyst through a combination of $Cu(OAc)_2$ and air.

In the case of the desymmetrization process, the palladacycle intermediate of type **II** is chiral, and the preferred formation of one of the enantiomer over the other must be attributed to steric clashing effects in the C−H activation step (**I** to **II**), as proposed for simple functionalization reactions.[14]

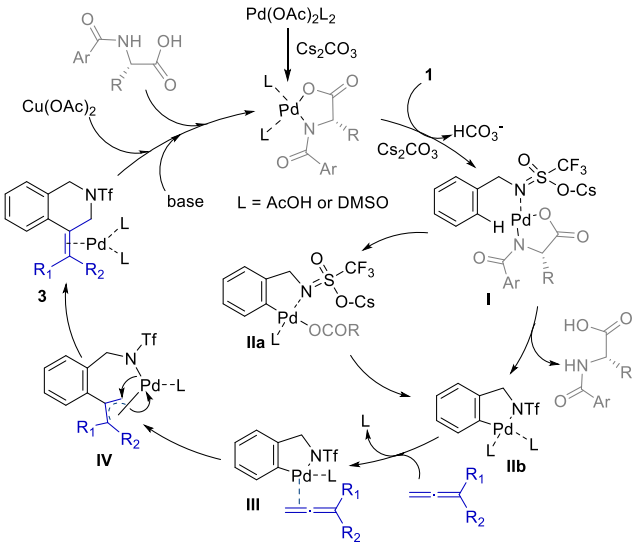
In conclusion, we have developed a straightforward access to highly valuable tetrahydroisoquinoline and tetrahydropyridine skeletons through a palladium-catalyzed formal (4+2) cycloaddition of benzyl and allylamines to allenes. The reaction relies on a Pd-catalyzed Csp^2−H activation, and presents excellent levels of chemo- and regioselectivity; being also highly appealing in terms of atom economy. More important,

Table 4. Enantioselective Pd(II)-Desymmetrization of Diarylmethyltriflamide[a,b]



[a]Conditions: 0.333 mmol of amides **1**, 0.167 mmol of allenes **2**, under air, 16 h. Isolated yields based on **2**. [b]Structure of the major product shown. [c]70 °C, 3 days. [d]0.167 mmol of triflamide **1g**, 0.333 mmol of allenes **2a** and **2d**. Yield based on **1g**. [e]Hydrogens omitted for clarity. Note: Ar represents the same aromatic ring than that undergoing the transformation, as corresponds for a symmetric substrate.

Scheme 2. Mechanistic Proposal



the annulation can be performed in an enantioselective fashion using prochiral diarylmethylamines, leading to enantiomeric

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ratios up to 98:2. This type of palladium-catalyzed annulative C−H activation/desymmetrization processes, which had not been previously reported, represents an important new addition to the armory of catalytic asymmetric methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b12636.

Experimental procedures and spectroscopic data for new compounds (PDF)
CIF file for compound **3ba** (CIF)
CIF file for compound **3ga** (CIF)

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Notes

The authors declare no competing financial interest.

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