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Intramolecular Umpolung Allylation of Imines

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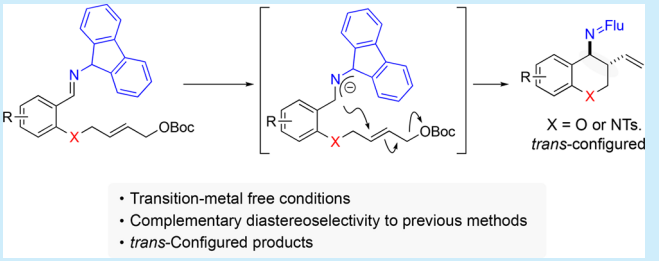
Supporting Information

ABSTRACT: An intramolecular umpolung allylation of imines is reported. This reaction occurs via the intermediacy of 2-azaallyl anions. It could proceed either under transition-metal-catalyzed conditions or under transition-metal-free conditions. Importantly, this approach afforded *trans*-3-vinyl-4-aminochromanes with high diastereoselectivity, while conventional, nonumpolung methods often display high *cis*-selectivity.



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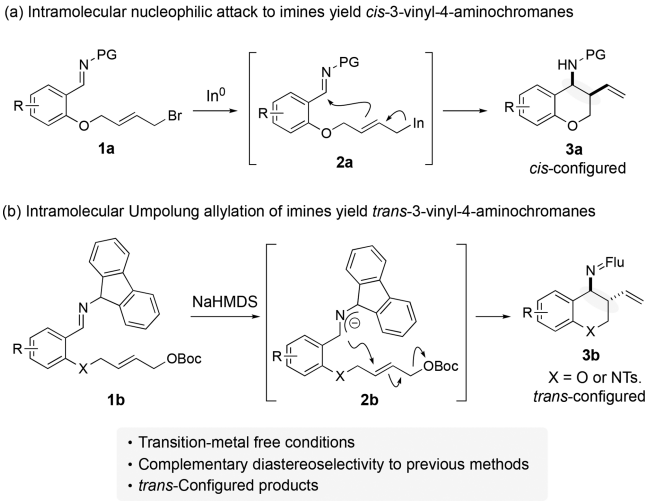
Nucleophilic attack on imines (as electrophiles) represents one of the most frequently used methods for the preparation of amines.[1] Recently, methods that employ imines as nucleophiles via the intermediacy of 2-azaallyl anions[2] (the umpolung[3] functionalization of imines) have attracted an increasing amount of attention as a new paradigm for amine synthesis.[4−9] This umpolung strategy could potentially avoid the generation and use of sensitive organometallic reagents and/or activated imine species. Meanwhile, this umpolung strategy gives products that readily lead to synthetically versatile primary amines. Moreover, the umpolung approach may yield products that are traditionally challenging to prepare. For example, we reported an iridium-catalyzed, tandem umpolung allylation of imine/2-aza-Cope rearrangement sequence to synthesize enantioenriched 1,4-disubstituted homoallylic amines, which are not readily accessible using previous methods.[8e,g]

The 4-aminochromanes are key structural units of many biologically active molecules and natural products,[11] such as cromakalim[11a] and LY3000328.[11d] Numerous groups[10] have reported the syntheses of these compounds by an intramolecular allylation approach, featuring the nucleophilic attack of the in situ generated allylmetal intermediate to imines. These methods yielded the valuable and versatile 3-vinyl-4-aminochromanes (Scheme 1) with high *cis*-selectivity. In continuation of our interest in the field of umpolung functionalization of imines, we wondered if this umpolung approach could be exploited to prepare 3-vinyl-4-aminochromanes as well. If realized, this method might eliminate the use of stoichiometric metal mediators and avoid the generation of (potentially) sensitive allyl halides. In this communication, we report that such intramolecular umpolung allylation of imines is feasible. Importantly, we have found that this transformation can proceed under transition-metal-free conditions. Moreover, this process is amenable to the preparation of both 3-vinyl-4-aminochromanes and 3-vinyl-4-aminotetrahydroquinolines. Lastly, our umpolung approach exhibits high *trans*-selectivity, while the previously reported, traditional methods exhibit high *cis*-selectivity.

Scheme 1. Methods for the Preparation of 3-Vinyl-4-aminochromanes: Previous Strategies (a) and This Work (b)



We commenced our study by utilizing *N*-fluorenyl imine tethered allylic carbonate **4** as a model substrate to optimize the reaction conditions. We initially employed palladium-based catalysts to effect this transformation due to their widespread use to activate allyl carbonates in allylic substitution reactions.[12] Indeed, exposure of **4** to $Pd(PPh_3)_4$ and NaHMDS in THF afforded the intramolecular cyclized product **5** in 20% yield (combined yield of two diastereoisomers) with 4:1 dr (*trans*/*cis*, Table 1, entry 1). Further screening of palladium sources and ligands revealed that the combination of

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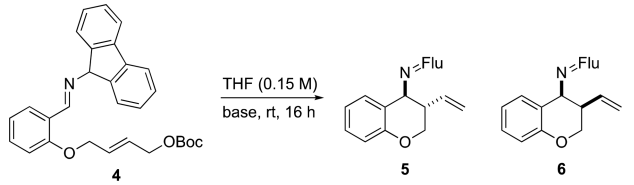
Table 1. Optimization of the Intramolecular Umpolung Allylation Reaction of Imine 4[a]



entry	catalyst	ligand	base	yield (%)[b]	dr (5:6)[c]
1	$Pd(PPh_3)_4$	none	NaHMDS	20	4:1
2	$PdCl_2{\cdot}(CH_3CN)_2$	PCy_3	NaHMDS	52	13:1
3	$PdCl_2$	PCy_3	NaHMDS	80	18:1
4	$[PdCl(allyl)]_2$	PCy_3	NaHMDS	42	3.6:1
5	none	none	NaHMDS	63	>20:1
6	none	none	LiHMDS	32	>20:1
7	none	none	KHMDS	17	>20:1
8	none	none	NaO^{t}Bu	27	>20:1
9	none	none	DBU	0	-
10[d]	none	none	NaHMDS	67	>20:1

[a]Reaction conditions: **4** (0.15 mmol), catalyst (6 mol % based on metal ions, if used), ligand (24 mol %, if used), base (1.05 equiv) in 1 mL of THF at room temperature for 16 h. [b]Determined by ^{1}H NMR analysis with 2-methynaphthalene as the internal standard. [c]Determined by ^{1}H NMR analysis of the crude reaction mixtures. [d]0.03 M in THF.

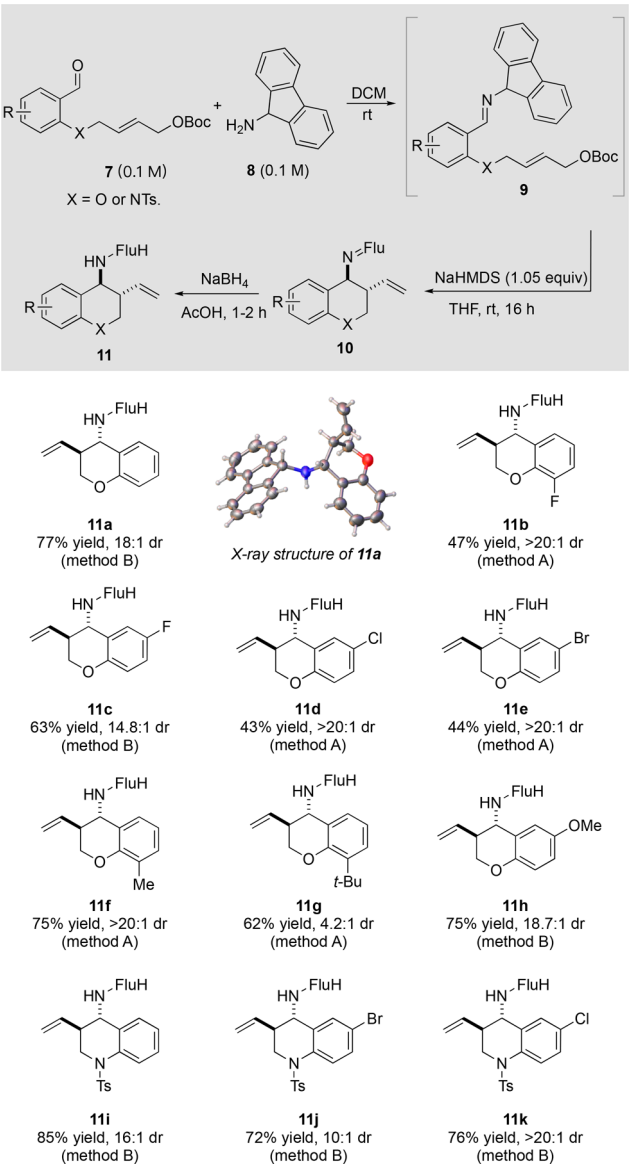
tricyclohexyl phosphine (PCy_3) and $PdCl_2$ gave better results in terms of yield as well as diastereoselectivity (80% yield, 18:1 dr, entry 3).

Interestingly, a control experiment showed that the reaction smoothly delivered **5** in 63% yield with >20:1 dr in the absence of transition metals (Table 1, entry 5). It is rare to see allyl carbonates function as electrophiles in transition-metal-free allylic substitution reactions. The efficient formation of **5** under our conditions is therefore remarkable. Other bases were found to be less efficient in promoting the reaction (entries 6−9). Reducing the reaction concentration resulted in a further slight increase in yield (Table 1, entry 10). Product **5** was reduced to give **11a** by treatment with $NaBH_4$, whose relative configuration was unambiguously determined by X-ray analysis. Notably, our method complements previous approaches in that it affords *trans*-substituted products.

With the above reaction conditions established, we explored the scope and limitations of this transformation, as summarized in Scheme 2. Conditions with or without the catalyst $PdCl_2$ were attempted, and the one with a higher yield was displayed (see results of both conditions in the Supporting Information). We highlight here that the 9-fluorenyl imine product **10** was readily obtained through a one-pot operation comprising the condensation of 9*H*-fluoren-9-amine **8** and substituted benzaldehyde **7** in dry dichloromethane, removal of the solvent (without purification), and addition of THF and NaHMDS. The 9-fluorenimine products (**10**) were reduced to afford 9-fluorenylamines (**11**).[6h] Alternatively, the products of the reactions could also be hydrolyzed to give primary amines and isolated as the corresponding *N*-Boc amines (see Supporting Information).[8e]

This reaction displayed decent substrate scope, affording the products in good yields (combined yields of three-step sequences) and excellent diastereoselectivities. For instance, substituents at various positions are tolerated. Aryl halides are compatible with either reaction conditions (**11b−e**). The

Scheme 2. Substrate Scope of Intramolecular Umpolung Allylation Reaction[a]



[a]The reactions were performed at 0.5 mmol scale. The reported yields are isolated yields of purified products. dr's were determined by ^{1}H NMR analysis of crude reaction mixture. Method A: NaHMDS, THF, rt, 16 h; Method B: $PdCl_2$ (5 mol %), PCy_3 (20 mol %), NaHMDS, THF, rt, 16 h. See SI for detailed reaction procedures.

substrates containing an electron-donating methoxy group (**11h**) furnished the products in good yield and with excellent diastereoselectivity. Due to the wide use of the 4-aminotetrahydroquinoline structural unit in biologically active molecules, such as (−)-martinellic acid,[13a] GSK1324726A,[13b] and torcetrapib,[13c] we extended the reaction system to the preparation of 3-vinyl-4-aminotetrahydroquinolines by replacing the ether unit with the corresponding amine unit. Under the optimal conditions, the desired allylation products were obtained in good yields (72%−85%) with high diastereoselectivities (**11i−11k**).

A model rationalizing the observed unusual, *trans*-selective stereochemistry of this reaction has been proposed in Figure 1. We reasoned that in the transition state (TS) **2b** leading to the

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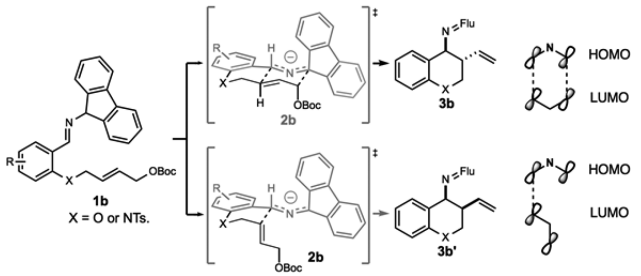

Figure 1. Transition state proposal for the intramolecular allylation reaction.

trans-product **3b** molecular orbital overlap between Cα and Cα' and between Cγ and Cγ' could be simultaneously achieved. Such favorable interaction between Cγ and Cγ' might lower the overall free energy of **2b**. On the other hand, in the TS that gives the *cis*-product, this secondary orbital overlap is inaccessible.

In summary, we have developed an umpolung allylation strategy to prepare 3-vinyl-4-aminochromanes and 3-vinyl-4-aminotetrahydroquinolines. This transformation exhibits high *trans*-selectivity, which is complementary to the existing *cis*-selective intramolecular cyclization processes. Importantly, our transformation could be effected by palladium catalysis or under transition-metal-free conditions. A model rationalizing the observed stereoselectivity is proposed. Further investigations regarding the scope and enantioselective variants of the current protocol are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02536.

Detailed experimental procedures, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1547232 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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