Enantio- and Diastereoselective Synthesis of Homoallylic α-Trifluoromethyl Amines by Catalytic Hydroalkylation of Dienes

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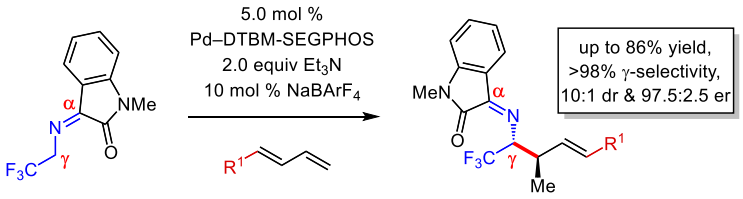
Abstract: We describe a strategy for the enantio- and diastereoselective synthesis of homoallylic α-trifluoromethyl amines by the catalytic hydroalkylation of terminal dienes. Trifluoromethyl-substituted isatin-derived azadienolate nucleophiles undergo γ-selective alkylation with a Pd–DTBM-SEGPHOS catalyst, which additionally promotes regioselective addition to the diene and delivers products in up to 86% yield, 10:1 dr, and 97.5:2.5 er.

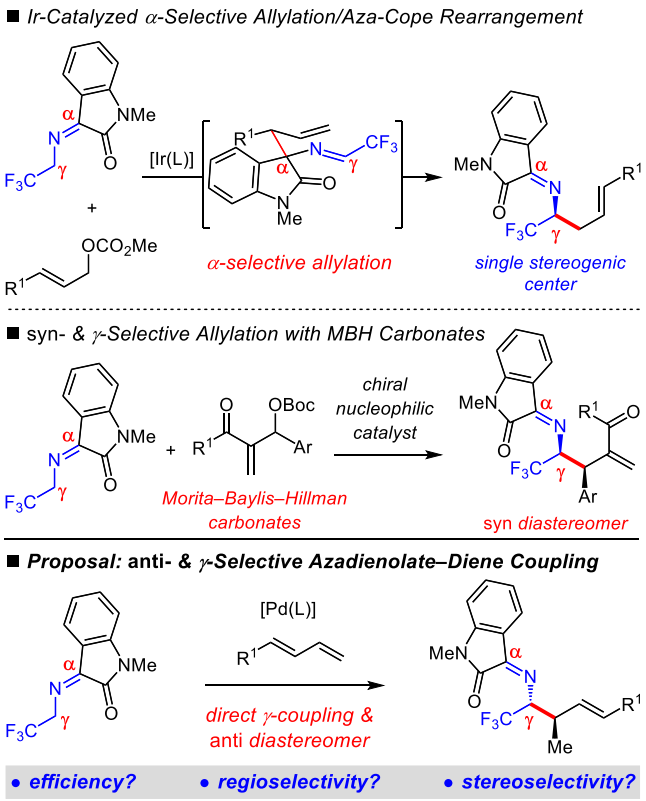
Keywords: hydroalkylation, dienes, homoallylic α-CF_3 amines, enantioselectivity, palladium

TOC graphic:



Chiral amines bearing an α-trifluoromethyl group hold a significant place among classes of medicinally important N-containing molecules. The CF_3 group modulates a number of pharmacological parameters, alters the amine basicity and polarity significantly, and stands in as a non-hydrolyzable amide surrogate.[1] Despite the beneficial properties this motif might impart upon drug-like molecules, methods for the catalytic enantioselective synthesis of α-trifluoromethyl amines are fairly uncommon, with most approaches to these enantioenriched compounds relying on chiral auxiliary chemistry.[2]

A valuable subset of these compounds are α-trifluoromethyl homoallylic amines. Recently, a number of groups have investigated allylic substitution approaches to these molecules utilizing azaallyl anion building blocks;[3] however, these strategies have led to a limited chemical space, including products with a single stereogenic center (transition metal-catalyzed reactions) or with products bearing two stereogenic centers exclusively in a *syn* relationship (nucleophilic organic molecule catalysts). For example, with an isatin[4] activating group for the nucleophile (Scheme 1), an Ir-catalyzed procedure gives rise to branch-selective coupling of the allylic carbonate exclusively at the azadienolate's α-position; however, this product spontaneously undergoes aza-Cope rearrangement to deliver a net γ-allylation, and as a result, the unsaturated amines bear only one stereogenic center.[4,5] Contrastingly, the same class of nucleophiles has been utilized in a γ-selective allylation with Morita–Baylis–Hillman-type allylic carbonates by employing a chiral nucleophilic catalyst (Scheme 1).[6] These coupling processes can yield homoallylic amines with vicinal *syn* stereogenic centers,[6a] but the product scope is additionally limited to aryl-substituted allylic centers and carbonyl-containing alkenes.[7]

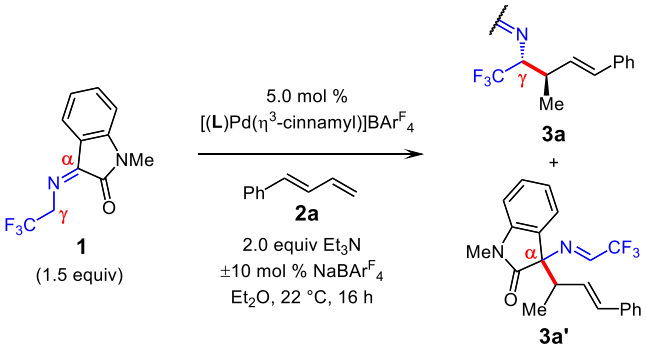


Scheme 1. Prior Catalytic Enantioselective α-CF_3 Homoallylic Amine Synthesis and Proposed Strategy

Given our longstanding interests in both umpolung synthesis of amines[8] and diene hydrofunctionalization reactions,[9] we envisioned that the merger of these strategies would allow

for the enantio- diastereo-, and regioselective preparation of α-CF_3 homoallylic amines that bear internal alkenes[9a] *and* vicinal stereogenic centers, potentially enabling the *anti* diastereomer to be accessed (Scheme 1). Several challenges had to be met and overcome for the successful realization of this idea. Primary among these was regioselectivity. In contrast to previous metal-catalyzed allylic substitution methods, our goal was to develop *a kinetically γ-selective allylation* of isatin azadienolates, obviating the aza-Cope rearrangement and thus giving rise to a fundamentally different product connectivity than would otherwise be available. Could a catalyst be found that is γ-selective and would this process still be efficient? Would the same catalyst also provide regioselectivity with respect to the diene? Finally, would such a catalyst allow for control of the relative and absolute stereochemistry of the homoallylic amine products? Only recently has a diene hydroalkylation that sets two stereogenic centers in one bond-forming event been reported.[10] Herein, we illustrate that Pd–DTBM-SEGPHOS promotes the γ-selective coupling of azadienolates with the terminal olefin of dienes, generating the *anti* diastereomer of homoallylic α-CF_3 amines with excellent levels of stereocontrol.[11]

Table 1. Optimization for γ-Selective Addition of an Isatin-Derived Azadienolate to Phenylbutadiene[a]



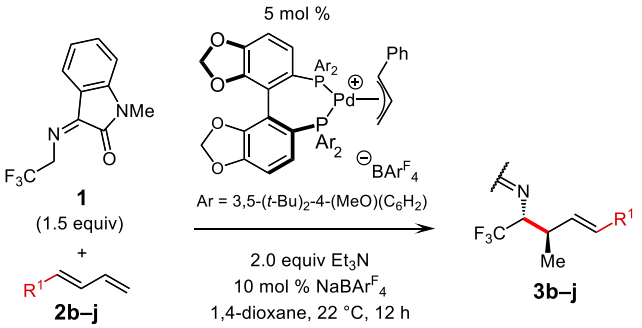
entry	L	$NaBAr^F_4$ (Y/N)	**3a**:**3a'**[b]	conv to **3a**/**3a'** (%)[b]	dr of **3a**[b]	er of **3a**[c]
1	BINAP	N	1:2.5	48	1:1	nd
2	MeO-BIPHEP	N	1:2.5	66	1.5:1	nd
3	DTBM-MeO-BIPHEP	N	>20:1	49	7:1	nd
4	SEGPHOS	N	1:1.1	30	3:1	nd
5	DM-SEGPHOS	N	1:1.5	38	3:1	nd
6	DTBM-SEGPHOS	N	>20:1	>98	9:1	91.5:8.5
7	DTBM-SEGPHOS	Y	>20:1	>98	9:1	93:7
8[d]	DTBM-SEGPHOS	N	>20:1	>98	8:1	94:6
9[d,e]	DTBM-SEGPHOS	Y	>20:1	97 (80)[f]	8:1	95:5

[a]Reactions run under N_2 with 0.15 mmol diene **2a** (0.75 M). [b]Determined by 376 MHz ^{19}F NMR spectroscopy of the unpurified mixture. [c]Determined by HPLC analysis of purified **3a**. [d]1,4-Dioxane as solvent. [e]Reaction for 12 h. [f]Isolated yield of purified **3a**. nd = not determined.

We initiated our investigations by exploring the coupling of *N*-trifluoroethyl imine **1** and phenylbutadiene **2a** (Table 1).[12] Whereas most ligands favor azadienolate α-alkylation product **3a′** under Pd catalysis, bis(phosphines) comprised of 3,5-di-*tert*-butyl-4-methoxy (DTBM) aryl

groups at phosphorus exclusively deliver the desired γ-alkylation product **3a** (compare entries 3 and 6 with 1–2 and 4–5).[13] Notably, the diastereomeric ratio for **3a** is also considerably higher with the more γ-selective catalysts, affording the *anti* diastereomer as the major isomer (entries 3 and 6). Use of DTBM-SEGPHOS provides the greatest conversion to **3a**, which is isolated in 9:1 dr and 91.5:8.5 er (entry 6).[14] We discovered that the enantioselectivity could be improved by the addition of 10 mol % $NaBAr^F_4$ (93:7 er, entry 7).[15] By switching the solvent from diethyl ether to 1,4-dioxane, γ-alkylation product **3a** is isolated in 80% yield, 8:1 dr, and 95:5 er (entry 9).

Table 2. Aryl Diene Scope in Azadienolate Coupling[a]



entry	product (**3**); R^1	conv to **3** (%);[b] yield of **3** (%)[c]	dr of **3**[b]	er of **3**[d]
1	**3b**; 4-(MeO)(C_6H_4)	87; 68	10:1	94:6
2	**3c**; 4-Cl(C_6H_4)	98; 75	7:1	90.5:9.5
3	**3d**; 4-(F_3C)(C_6H_4)	94; 74	8:1	90:10
4	**3e**; 3-Me(C_6H_4)	89; 72	6:1	93:7
5[e]	**3f**; 2-Me(C_6H_4)	63; 59	2:1	92.5:7.5
6	**3g**; 2-naphthyl	94; 62	8:1	94:6
7	**3h**; 3,4-dioxolato(C_6H_3)	94; 86	10:1	91.5:8.5
8	**3i**; 2-furyl	69; 59	8:1	93:7
9	**3j**; 3-pyridyl	83; 82	7:1	94:6

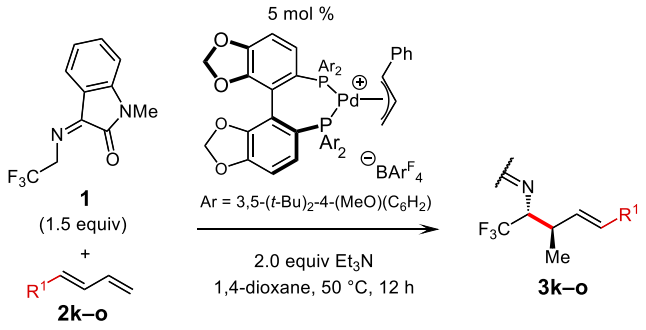
[a]Reactions run under N_2 with 0.15 mmol diene **2** (0.75 M). [b]Determined by 376 MHz ^{19}F NMR or 400 MHz ^1H NMR spectroscopy of the unpurified mixture. [c]Isolated yield of purified **3**. [d] Determined by HPLC analysis of purified **3**. [e]Reaction run without $NaBAr^F_4$; 9:1 **3f**:**3f′**.

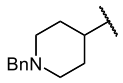
Taking the conditions in Table 1, entry 9 as optimal, we next explored the scope of aryl-substituted terminal dienes for coupling with **1** (Table 2). Both electron-rich (e.g., entries 1 and 6–7) and electron-poor (entries 2–3) dienes generate the homoallylic amine products ≥87% conversion, ≥7:1 dr, and with moderate to good enantioselectivity. Heterocycles are tolerated, with furyl-substituted **3i** (entry 8) and pyridyl-containing **3j** (entry 9) isolated in good yields and stereoselectivities. The majority of dienes lead exclusively to the γ-alkylation product; however, an *ortho* substituent on the arene results in a more sluggish reaction (44% conversion in 12 h) that furnishes approximately 10% α-coupling of the azadienolate (entry 5). Improving reaction efficiency required the omission of $NaBAr^F_4$, and while diastereoselectivity was lower, enantioselectivity remained high (92.5:7.5 er). In all, aryl-substituted dienes readily participate in

couplings with **1** at room temperature, affording homoallylic α-trifluoromethyl amines **3b–j** in 59–86% yield.

Alkyl-substituted terminal dienes are also effective coupling partners; however, the Pd–DTBM-SEGPHOS-catalyzed processes with imine **1** require elevated temperature (50 °C) to proceed effectively (Table 3). Consequently, we also omitted the $NaBAr^F_4$ additive to enable the reaction to proceed at a higher rate. Both linear (entries 1–3) and α-branched (entries 4–5) dienes participate in the reactions, affording homoallylic amines **3k–o** in 43–84% yield in up to 4:1 dr and 91:9 er. Products derived from isomerization of the diene along the alkyl chain ("chain walking") prior to enolate addition could not be detected, including with phenethyl **2k** or heptadienoate **2m**. Alkyl dienes largely or solely lead to γ-alkylation of the azadienolate although it is notable that piperidine **20** affords ca. 9% α product **3o′**. We also observed roughly 8% of an additional γ-alkylation product **3k″** with phenethyl diene **2k**. Homoallylic amine **3k″** bears a different connectivity with respect to the diene-derived fragment, and a series of experiments suggest that **3k″** is formed from the aza-Cope rearrangement of α-alkylation product **3k′**.[16]

Table 3. Azadienolate–Alkyl Diene Coupling Scope[a]

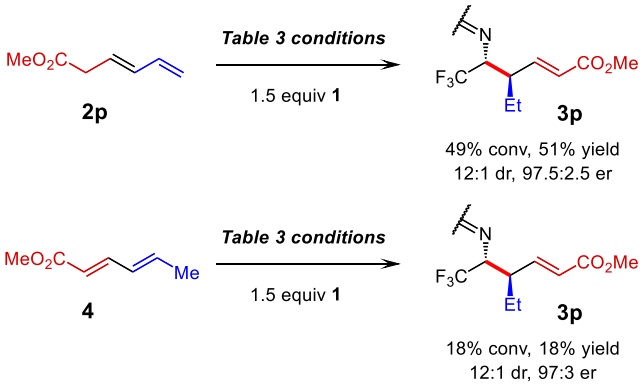


entry	product (**3**); R^1	conv to **3** (%); yield of **3** (%)[c]	dr of **3**[b]	er of **3**[d]
1[e]	**3k**; $Ph(CH_2)_2$	82; 69	4:1	88:12
2	**3l**; *n*-hexyl	65; 60	4:1	81.5:18.5
3	**3m**; $EtO_2C(CH_2)_2$	84; 83	3:1	91:9
4	**3n**; Cy	61; 43	3:1	90:10
5[f]	**3o**; 	81; 84	3:1	86.5:13.5

[a]Reactions run under N_2 with 0.15 mmol diene **2** (0.75 M). [b]Determined by 376 MHz ^{19}F NMR or 400 MHz ^1H NMR spectroscopy of the unpurified mixture. [c]Isolated yield of purified **3**. [d] Determined by HPLC analysis of purified **3**. [e]A 10:1 mixture of γ-alkylation products **3k** and **3k″** was formed; see footnote [16]. [f]11:1 **3o**:**3o′**.

Intriguingly, in the course of our alkyl diene studies, we discovered that hexadienoate **2p** (Scheme 2) undergoes diene isomerization into conjugation with the ester prior to its coupling with **1**, furnishing the ethyl-substituted stereogenic center of homoallylic amine **3p**. The process is reasonably efficient, with the α-CF_3 amine obtained in 51% yield, 12:1 dr, and 97.5:2.5 er.

Comparatively, its internal diene analogue **4** also delivers acrylate **3p** with similar levels of stereoselectivity but lower conversion.



Scheme 2. Isomerization/Alkylation of 3,5-Hexadienoate and Comparison to its Internal Diene Isomer

We have explored a number of additional reaction partners to expand the scope of the hydrofunctionalization (Figure 1). Imine **5** was tested in a coupling with diene **2a** in order to access α-difluoromethyl amines, but unfortunately the nucleophile undergoes complete decomposition without alkylation. Substituted imines, such as **6**, would form products bearing tetrasubstituted stereogenic centers[5,6b,11] but were unreactive. Other dienes were also investigated. Alcohol- and silyl ether-containing alkyl dienes **2q** and **2r** lead to a complex mixture of products, which we surmise to be a combination of the desired γ-alkylation **3**, the regiomeric α-alkylation **3′**, and the aza-Cope rearrangement products **3′′**, all as a mixture of diastereomers, rather than products attributable to chain walking.

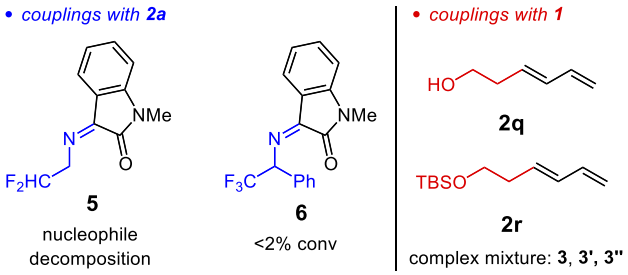
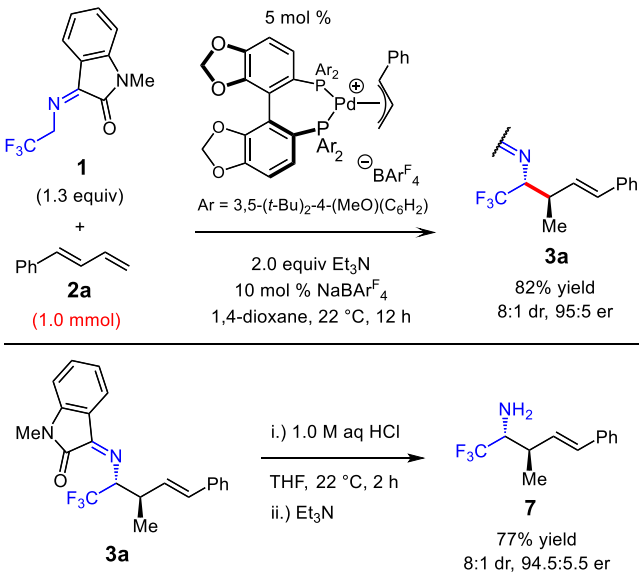


Figure 1. Limitations in Reaction Partners

The diene hydroalkylation with imine **1** can be performed on a 1.0 mmol scale to furnish the α-trifluoromethyl isatin-protected homoallylic amine **3a** in 82% yield (Scheme 3). Additionally, hydrolysis of the isatin moiety under mildly acidic conditions delivers the free amine **7** in 77% yield.



Scheme 3. Scale Up of Azadienolate Hydroalkylation and Product Imine Hydrolysis

Catalytic enantioselective diene hydrofunctionalization provides an enabling route toward highly valuable chemical building blocks that are not readily prepared by other methods. Here, in combination with imine umpolung,[3] we have shown that important homoallylic α-trifluoromethyl amines bearing contiguous stereogenic centers and an internal olefin can be accessed for the first time. Utilizing an isatin auxiliary, we have discovered that, in contrast to other transition metal-catalyzed processes, palladium ligated with DTBM-SEGPHOS allows for regioselective γ-alkylation of the derived azadienolate, generating the *anti* diastereomer of the homoallylic α-CF_3 amines with high levels of stereocontrol. This catalytic process should open up new chemical space for drug discovery.

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Conflict of Interest Statement

The authors declare no conflict of interest.

Supporting Information

Supporting information for this article can be found online at: (insert link here)

X-ray crystallographic data for **3c** has been deposited in the CCDC (1978720).

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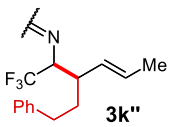
[12] For additional screening data, see the Supporting Information.

[13] The transformations in Table 1 utilize pre-formed Pd–bis(phosphine) complex derived from $[Pd(\eta^3\text{-cinnamyl})Cl]_2$, bis(phosphine), and $NaBAr^F{}_4$. When conducting reactions directly with *in situ*-generated catalyst, we observe a significant induction period in the reaction that is avoided by employing isolated complex. See the Supporting Information for further details.

[14] Pd–DTBM-SEGPHOS has been shown to be the optimal catalyst in a handful of enantioselective diene hydrophosphinylation reactions; see: S.-Z. Nie, R. T. Davison, V. M. Dong. Enantioselective Coupling of Dienes and Phosphine Oxides. *J. Am. Chem. Soc.* **2018**, *140*, 16450.

[15] Although $NaBAr^F{}_4$ improves enantioselectivity, it greatly reduces the reaction rate. Under the conditions shown in Table 1, entry 6 without $NaBAr^F{}_4$, the reaction is complete within 6 h, but longer reaction times are needed the more $NaBAr^F{}_4$ is added. The data in Table 1 are all shown for 16 h reaction time for comparative purposes. See the Supporting Information for additional details.

[16] See the Supporting Information for a detailed discussion.



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