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

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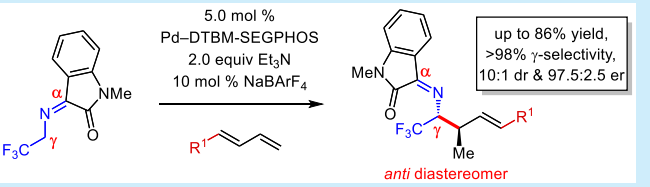
ABSTRACT: We describe a strategy for the enantio- and diastereoselective synthesis of homoallylic α-trifluoromethyl amines by the catalytic hydroalkylation of terminal dienes. Trifluoromethyl-substituted isatin-derived azadienolate nucleophiles undergo γ-selective alkylation with a Pd–DTBM-SEGPHOS catalyst, 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.



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] 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. As a result, the unsaturated amines bear only one stereogenic center.[4,5] The same class of nucleophiles have 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] however, the product scope is limited to aryl-substituted allylic centers and carbonyl-containing alkenes.[7,8]

Given our longstanding interests in both umpolung synthesis of amines[9] and diene hydrofunctionalization reactions,[10] 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 vicinal stereogenic centers *and* internal alkenes,[10a] 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.

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

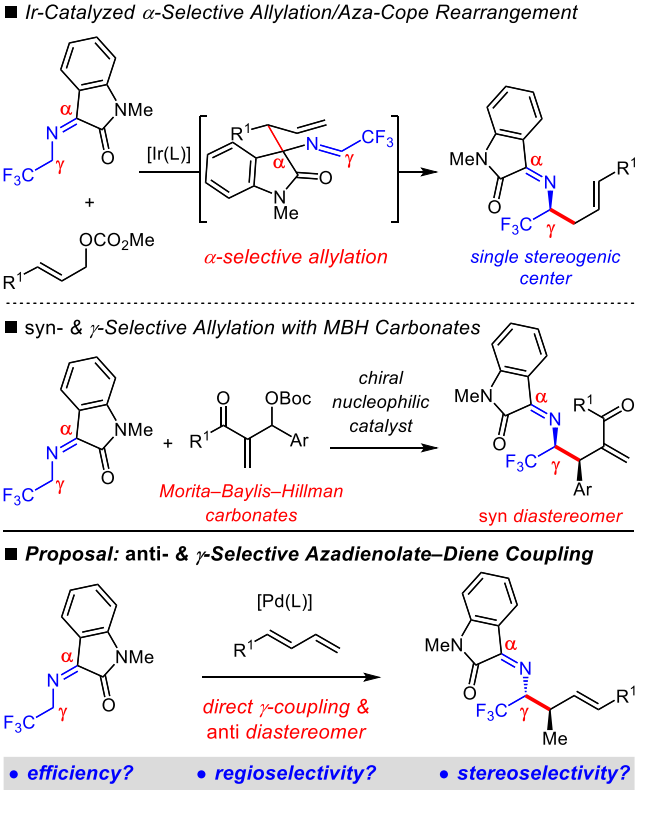


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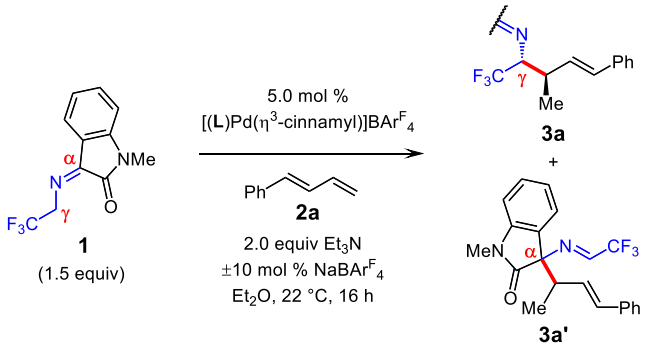
Table 1. Optimization for γ-Selective Addition of an Isatin-Derived Azadienolate to Phenylbutadiene[a]



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

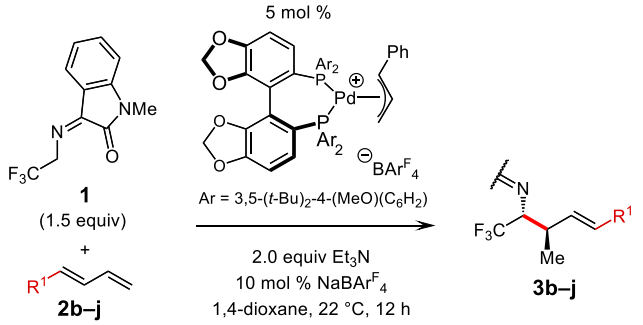
[a]Reactions run under N_2 with 0.15 mmol of diene **2a** (0.75 M). [b]Determined by 376 MHz ^{19}F NMR spectroscopy of the unpurified mixture. [c]Determined by HPLC analysis of purified **3a**. [d]1,4-Dioxane as solvent. [e]Reaction for 12 h. [f]Isolated yield of purified **3a**. nd = not determined.

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.[11] 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.[12]

We initiated our investigations by exploring the coupling of *N*-trifluoroethyl imine **1** and phenylbutadiene **2a** (Table 1).[13] 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 entries 1–2 and 4–5).[14] 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).[15] We discovered that the enantioselectivity could be improved by the addition of 10 mol % $NaBAr^F_4$ (93:7 er, entry 7).[16] By switching the solvent from diethyl ether to 1,4-dioxane, the γ-alkylation product **3a** is isolated in 80% yield, 8:1 dr, and 95:5 er (entry 9).

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 with ≥87% conversion, ≥7:1 dr, and moderate to good enantioselectivity. Heterocycles are tolerated, with furyl-substituted **3i** (entry 8) and pyridyl-containing **3j** (entry 9) isolated in good yields and stereo-

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



entry	product (3); R^1	conv to 3a [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 of 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′**.

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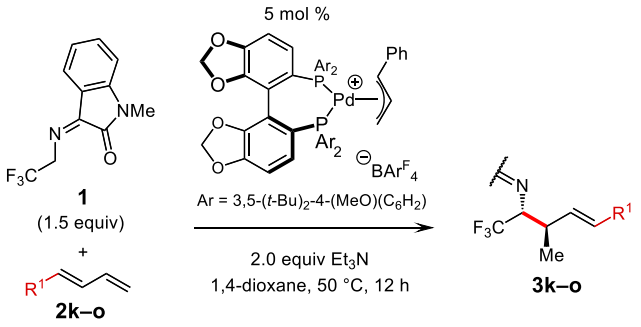
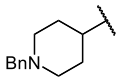
Org. Lett. XXXX, XXX, XXX–XXX

selectivities. 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

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



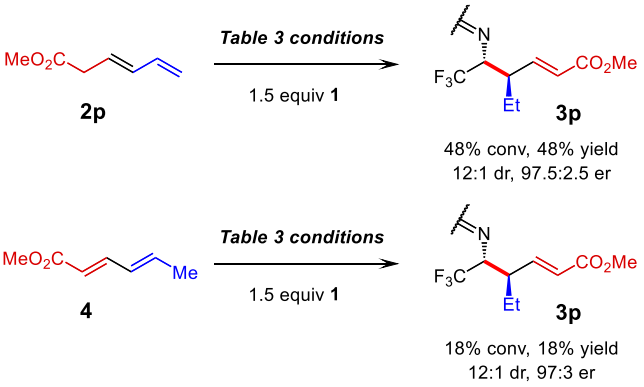
entry	product (**3**); R^1	conv to **3** (%);[b] yield of **3** (%)[c]	dr of **3**[b]	er of **3**[d]
1[e]	**3k**; $Ph(CH_2)_2$	82; 69	4:1	88:12
2	**3l**; *n*-hexyl	65; 60	4:1	81.5:18.5
3	**3m**; $EtO_2C(CH_2)_2$	84; 83	3:1	91:9
4	**3n**; Cy	61; 43	3:1	90:10
5[f]	**3o**; 	83; 83	3:1	86.5:13.5

[a]Reactions run under N_2 with 0.15 mmol of 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 ref 17. [f]11:1 **3o**:**3o′**.

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 43–83% 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 **2o** 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′**.[17]

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

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



efficient, with the α-CF_3 amine obtained in 48% 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.

We have explored a number of additional reaction partners to expand the scope of the hydrofunctionalization (Figure 1).

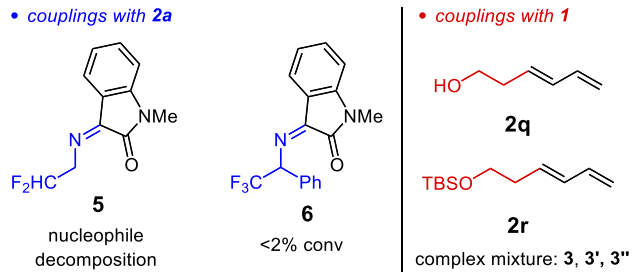


Figure 1. Limitations in Reaction Partners.

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,8] 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.

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.

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, generat-

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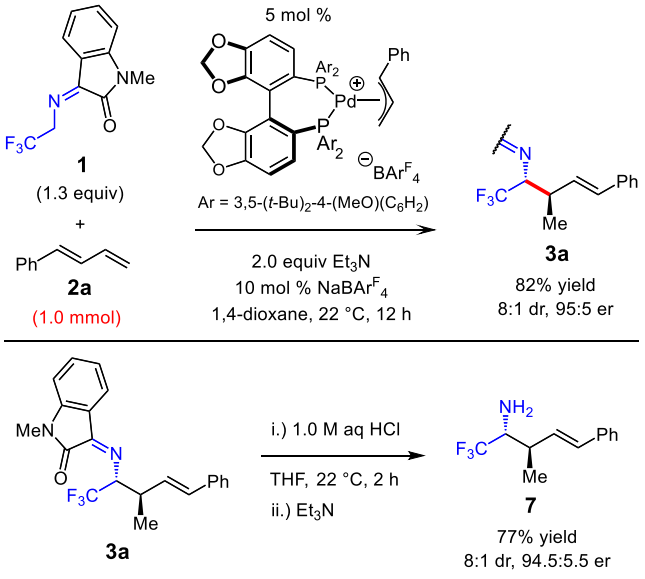
Org. Lett. XXXX, XXX, XXX–XXX

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



ing 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00342.

Experimental procedures, analytical data for new compounds, X-ray crystallographic data, and NMR spectra (PDF)

Accession Codes

CCDC 1978720 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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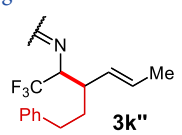
(13) For additional screening data, see the Supporting Information.

(14) The transformations in Table 1 utilize a preformed 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 an isolated complex. See the Supporting Information for further details.

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

(16) 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.

(17) See the Supporting Information for a detailed discussion.



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