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A Divergent Approach to the Synthesis of 3-Substituted-2-pyrazolines: Suzuki Cross-Coupling of 3-Sulfonyloxy-2-pyrazolines

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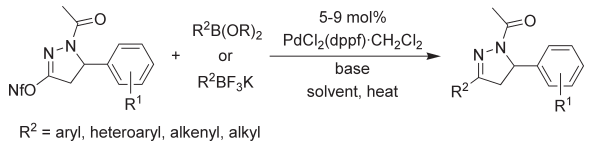
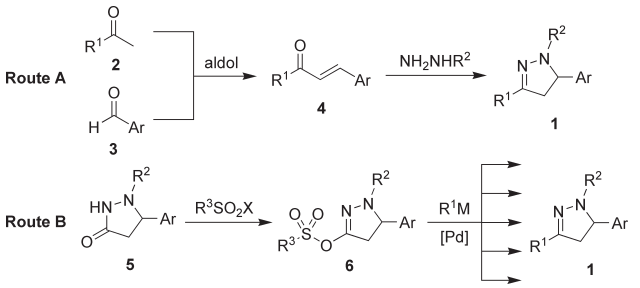


The efficient Suzuki cross-coupling of pyrazoline nonaflates with organoboron reagents was achieved to afford diverse 3-substituted-2-pyrazolines in excellent yield. The nonaflates displayed improved reactivity over the corresponding triflates and smoothly coupled to a variety of aryl- and heteroarylboronic acids. This process and its broad scope constitute a rapid, divergent strategy for the synthesis of elaborated 2-pyrazolines that are not readily obtained via conventional methods.

The 2-pyrazoline ring system has attracted significant interest in organic and medicinal chemistry over the past several decades. Scaffolds containing the 2-pyrazoline (4,5-dihydropyrazole) heterocycle have demonstrated a wide range of biological activity, including anticancer activity through the inhibition of kinesin spindle protein,[1] CB_1 receptor antagonism for obesity,[2] monoamine oxidase inhibition for depression,[3] and a host of other antibacterial, antiviral, and anti-inflammatory activities.[4] During the course of a recent medicinal chemistry program, we required access to diverse 3-substituted-2-pyrazolines (**1**, Scheme 1). We sought a strategy that would enable rapid exploration of structure−activity relationships through the late-stage, divergent installation of different C-3 substituents. Several synthetic methods exist for the preparation of pyrazolines, such as the condensation of hydrazines with α,β-unsaturated carbonyl compounds and the dipolar cycloaddition of nitrile imines with activated olefins.[5] The existing routes were not ideal for our purposes, as they typically fix the pyrazoline substituents prior to ring formation. Route A (Scheme 1) illustrates this limitation as it relates to the reaction of hydrazines with chalcones (**4**), where the C-3 and C-5 substituents are set in the aldol condensation that precedes cyclization. We decided to pursue an alternative strategy (Route B) that is the subject of this Note—the palladium-catalyzed cross-coupling of 3-sulfonyloxy-2-pyrazolines (**6**, from pyrazolidinones **5**) with organoboron reagents and other organometallics.

SCHEME 1. Strategies for Preparing 3-Substituted-2-pyrazolines



Despite the prevalence of transition metal-catalyzed cross-coupling reactions of alkenyl, aryl, and heteroaryl (i.e., pyridyl) halides and pseudohalides, those involving imidoyl halides and pseudohalides are rare. The limited examples that are known include the cross-coupling of imidoyl chlorides or triflates with alkynes,[6] stannanes,[7] Grignard reagents,[8] organozinc reagents,[9] and boronic acids.[10] A single report exists concerning the Suzuki cross-coupling of a 3-chloro-2-pyrazoline with boronic acids; however, the harsh reaction conditions ($POCl_3$) required to prepare the imidoyl chloride substrate limit the scope of this method.[11] Nonetheless, this suggested that the previously unexplored pyrazoline sulfonates **6**—which could be prepared through mild, broadly applicable conditions—could function in Suzuki cross-couplings and other palladium-catalyzed C−C bond formations.

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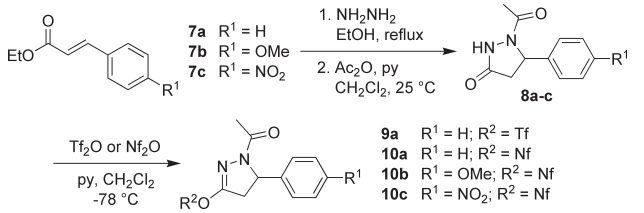
SCHEME 2. Preparation of 3-Sulfonyloxy-2-pyrazolines

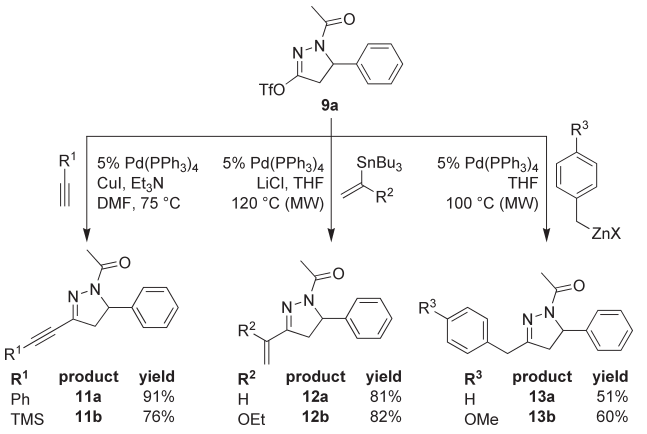


The pyrazoline sulfonates necessary for the exploration of this methodology were synthesized according to Scheme 2. Cinnamates **7a**−**c** were condensed with hydrazine in refluxing EtOH; the resulting pyrazolidinones were subsequently acetylated with acetic anhydride to provide **8a**−**c**.[12] The pendant aryl group and *N*-acetyl capping group were chosen due to the preponderance of the 1-acyl-3,5-diarylpyrazoline core among biologically active pyrazolines.[1,3,4] Pyrazolidinones **8a**−**c** were smoothly reacted with the appropriate sulfonic anhydride (Tf_2O or Nf_2O)[13] to afford triflate **9a** and nonaflates **10a**−**c** via exclusive *O*-sulfonylation.

Although the primary emphasis of this work was on the Suzuki cross-coupling of these substrates (vide infra), our attention initially focused on a brief investigation of the general cross-coupling scope of pyrazoline sulfonates. As summarized in Scheme 3, triflate **9a** was effective in Sonogashira, Stille, and Negishi cross-couplings. Sonogashira coupling of **9a** with phenylacetylene or trimethylsilylacetylene under standard conditions[14] provided 3-alkynylpyrazolines **11a**,**b** in good yield (91%, 76%). Similarly, 3-alkenylpyrazolines **12a**,**b** were generated in high yield (81−82%) through Stille coupling of **9a** with the corresponding vinylstannanes.[15] Negishi coupling[16] of **9a** with benzyl zinc halides under microwave conditions[17] allowed for the formation of 3-benzylpyrazolines **13a**,**b** in moderate yield (51−60%).[18] Few reports exist concerning the preparation of 3-alkenyl-, 3-alkynyl-, and 3-benzylpyrazolines, and their synthesis by existing methods is neither general nor trivial.[19] The rapid preparation of these diverse, rare structures from a common intermediate illustrates the utility of this method. The alkynyl and alkenyl groups of **11a**,**b** and **12a**,**b** also provide useful functional handles for further manipulation.

The Suzuki cross-coupling[20] of 3-sulfonyloxy-2-pyrazolines was of particular interest due to the extensive availability and synthetic accessibility of organoboron reagents. Such a process would provide rapid access to 3-heteroarylpyrazolines and allow incorporation of heterocycles commonly seen in medicinal chemistry. With this in mind,

SCHEME 3. Sonogashira, Stille, and Negishi Cross-Coupling of 9a



R1	product	yield
Ph	11a	91%
TMS	11b	76%

R2	product	yield
H	12a	81%
OEt	12b	82%

R3	product	yield
H	13a	51%
OMe	13b	60%

the reaction of **9a** with 3-pyridineboronic acid (**14a**) was employed as a model system to optimize the cross-coupling (Table 1). Initial results were not encouraging, as a variety of conditions failed to provide appreciable yields of **15a** (entries 1−6). These included Suzuki's initial triflate protocol[21] (entry 1), as well as the versatile conditions of Buchwald[22] (entry 4) and Fu[23] (entries 5−6) utilizing electron-rich, hindered phosphines. Additionally, Dvorak's conditions for the cross-coupling of pyrazole triflates (entry 7) afforded only a 20% yield of the desired product.[24] A similar yield of **15a** was achieved under more traditional Suzuki conditions,[20] with $Pd(PPh_3)_4$ as catalyst, Na_2CO_3 as base, and toluene/EtOH/H_2O (3:1:1) as solvent (entry 8, 22%). Performing this reaction in the microwave afforded no advantage in yield (entry 9), but the reaction time was dramatically shortened to only 10 min (as determined by the consumption of **9a**).[25] In nearly all cases (entries 1−14), the major species observed was pyrazolidinone **8a**, the product of triflate hydrolysis. Switching to dioxane/H_2O as solvent (entry 10) led to increased hydrolysis, and no conversion (exclusively **9a**) was seen when water was omitted (entry 12). Although the addition of Bu_4NBr had no effect (entry 11), LiCl led to a modest improvement in yield (entry 13, 32%).[20a] Similar results were seen with an alternative catalyst, $PdCl_2(dppf)\cdot CH_2Cl_2$ (entry 14).

Given that the key side reaction responsible for the low yields of **15a** was triflate hydrolysis, replacement of the triflate with a nonaflate (**10a**) was pursued as a mitigation strategy. Several studies have demonstrated the utility of alkenyl and aryl nonaflates in various cross-coupling reactions.[26] Evidence suggests that nonaflates are more resistant to O−S hydrolysis[27] and display enhanced reactivity in

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(17) Nearly equivalent results were obtained when the Stille and Negishi coupling reactions were performed thermally; slightly shorter reaction times and convenience encouraged use of the microwave.
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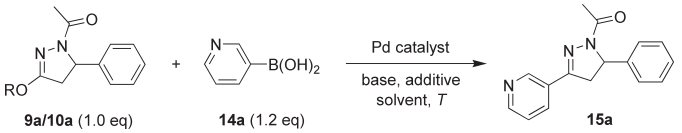
TABLE 1. Optimization of Suzuki Cross-Coupling with Pyrazoline Sulfonates



9a/10a (1.0 eq) **14a** (1.2 eq) **15a**

entry	R	mol % catalyst	base (equiv)	additive (equiv)	solvent	*T* (°C)	time[a]	yield[b] (%)
1	Tf	5% $Pd(PPh_3)_4$	K_3PO_4 (3)		dioxane	85	3 h	< 5
2	Tf	10% $Pd(P^tBu_3)_2$	K_3PO_4 (3)		toluene	70	2 h	< 5
3	Tf	10% $Pd(OAc)_2$/15% X-Phos	K_3PO_4 (3)		THF	70	2 h	< 5
4	Tf	2% Pd_2dba_3/8% S-Phos	K_3PO_4 (2)		1-butanol	100	18 h	< 5
5	Tf	10% $Pd(OAc)_2$/12% $Cy_3PH\cdot BF_4$	KF (3.3)		THF	80	1 h	0
6	Tf	5% Pd_2dba_3/10% $^tBu_3PH\cdot BF_4$	KF (3.3)		THF	90	18 h	0
7	Tf	8% $PdCl_2$(dppf)/4% dppf	K_3PO_4 (3)		dioxane	100	18 h	20
8	Tf	5% $Pd(PPh_3)_4$	Na_2CO_3 (3)		toluene/EtOH/H_2O (3:1:1)	100	2 h	22
9	Tf	5% $Pd(PPh_3)_4$	Na_2CO_3 (3)		toluene/EtOH/H_2O (3:1:1)	120 (MW)	10 min	20
10	Tf	5% $Pd(PPh_3)_4$	Na_2CO_3 (2)	- -	dioxane/H_2O(3:1)	120 (MW)	10 min	6
11	Tf	5% $Pd(PPh_3)_4$	Na_2CO_3 (2)	Bu_4NBr (0.1)	toluene/EtOH/H_2O (3:1:1)	120 (MW)	10 min	20
12	Tf	5% $Pd(PPh_3)_4$	Na_2CO_3 (2)	Bu_4NBr (0.1)	toluene	120 (MW)	10 min	0
13	Tf	5% $Pd(PPh_3)_4$	Na_2CO_3 (3)	LiCl (3)	toluene/EtOH/H_2O (3:1:1)	120 (MW)	10 min	32
14	Tf	5% $PdCl_2$(dppf)$\cdot CH_2Cl_2$	Na_2CO_3 (3)	LiCl (3)	toluene/EtOH/H_2O (3:1:1)	120 (MW)	10 min	32
15	Nf	5% $Pd(OAc)_2$/20% PPh_3	K_2CO_3 (1.5)		DMF	75	18 h	0
16	Nf	5% $Pd(PPh_3)_4$	Na_2CO_3 (3)		toluene/EtOH/H_2O (3:1:1)	120 (MW)	10 min	87
17	Nf	5% $Pd(PPh_3)_4$	Na_2CO_3 (3)		dioxane/H_2O(3:1)	120 (MW)	10 min	21
18	Nf	5% $PdCl_2$(dppf)$\cdot CH_2Cl_2$	Na_2CO_3(3)		toluene/EtOH/H_2O (3:1:1)	120 (MW)	10 min	90
19	Nf	5% $PdCl_2$(dppf)$\cdot CH_2Cl_2$	Na_2CO_3 (3)		toluene/EtOH/H_2O (3:1:1)	100	2 h	84

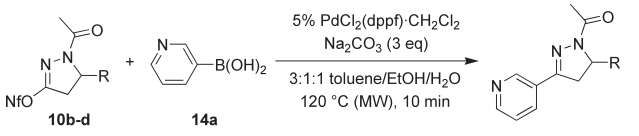
[a]Reactions stirred at indicated temperature until complete (or conversion ceased). [b]Isolated yield of chromatographically pure **15a** (yields < 5% determined by LC/MS).

cross-couplings compared to triflates.[26e] Conditions previously reported for nonaflate Suzuki couplings were not suitable for this reaction, affording none of the desired pyrazoline **15a** (entry 15).[26f,g] A dramatic improvement in yield was seen when returning to the $Pd(PPh_3)_4/Na_2CO_3$ conditions previously applied to the triflate (entry 16), whereby an 87% yield of **15a** was obtained. Importantly, only trace amounts of cleavage product **8a** were detectable by LC/MS analysis. $PdCl_2(dppf)\cdot CH_2Cl_2$ was a slightly superior catalyst and provided the optimum yield of **15a** (90%, entry 18). The cross-coupling could also be performed thermally at the cost of increased reaction time and a slight decrease in yield (84%, entry 19).

The newly optimized Suzuki cross-coupling conditions for nonaflate **10a** were then applied to various boronic acids and esters (Table 2). The scope was found to be extensive, as a diverse set of boronic acids and esters uniformly underwent cross-coupling with **10a** in the microwave to afford the desired 3-substituted pyrazolines **15a**−**t** in excellent to nearly quantitative yields (78−97%). The cross-coupling conditions were tolerant of electron-poor (entries 2−4), electron-rich (entries 5−6), and hindered (entry 7) arylboronic acids, as well as an alkenylboronic acid (entry 20). Importantly, a wide variety of heteroarylboronic acids (entries 9−14 and 17−19) and esters (entries 15 and 16) were effectively coupled to **10a** under these conditions, providing convenient access to pyrazolines with pyridine, pyrimidine, furan, thiophene, pyrazole, and other heterocyclic substituents at C-3. Of the boronic acids explored, only 2-pyridineboronic acids—routinely challenging Suzuki substrates—failed in the cross-coupling.

Not surprisingly, modification of the distal (C-5) substituent of the nonaflate substrate was also well-tolerated in the cross-coupling (Scheme 4). Nonaflates with functionalized aryl substituents (**10b**,**c**) or an alkyl-linked moiety (benzyl,

SCHEME 4. Suzuki Cross-Coupling of Nonaflates 10b−d



10b-d **14a**

R	nonaflate	product	yield (%)
p-$MeOC_6H_4$	**10b**	**15u**	96
p-$O_2NC_6H_4$	**10c**	**15v**	92
$PhCH_2$	**10d**	**15w**	90

10d[28]) were efficiently coupled with **14a** to provide 3-(3-pyridyl)pyrazolines **15u**−**w** in excellent yield (90−96%), further demonstrating the generality of this strategy for the synthesis of substituted pyrazolines.

To expand the utility of this Suzuki cross-coupling, a preliminary exploration into the cross-coupling of **10a** with potassium organotrifluoroborates was undertaken. The advantages of organotrifluoroborates are well-known, as they are highly stable, display improved reaction stoichiometry, and often offer functionality not available from boronic acids and esters (e.g., alkyltrifluoroborates).[29] This versatility has made trifluoroborates compelling substrates for Suzuki-type coupling reactions.[30] Modification of the pyrazoline nonaflate Suzuki conditions was required to achieve facile cross-coupling with organotrifluoroborates. The optimal conditions for the coupling of these species with **10a** is shown in Scheme 5. In concurrence with Molander,[30a−c] $PdCl_2(dppf)\cdot CH_2Cl_2$

(28) **10d** was prepared according to Scheme 2 (see the Supporting Information).

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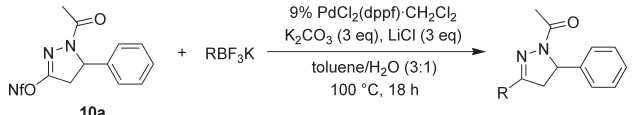
SCHEME 5. Cross-Coupling of 10a with Organotrifluoroborates



R	product	yield (%)
$PhCH_2$	**13a**	73
$PhCH_2CH_2$	**16a**	55
$^tBuO_2CCH_2CH_2$	**16b**	32
p-$CH_3C_6H_4$	**16c**	87

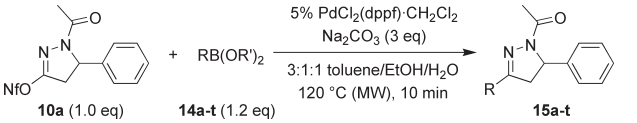
was found to be an efficient catalyst. The use of toluene/H_2O as solvent was essential; no product was seen with toluene/EtOH/H_2O, THF/H_2O, or nonaqueous solvent systems. The best results were obtained with K_2CO_3 as base, and the addition of LiCl (3 equiv) consistently enhanced yields. In contrast to the coupling with boronic acids, thermal conditions (100 °C, 18 h) generally provided higher conversions and greater yields than the microwave. Under these conditions, several trifluoroborates were successfully coupled to **10a** in moderate to good yield (32−87%).[31] These included primary alkylborates with pendant aryl or ester[32] groups (**13a**, **16a**,**b**) and an arylborate (**16c**). The cross-coupling of $PhCH_2BF_3K$ presents a higher yielding alternative to the Negishi coupling in Scheme 3. Furthermore, reports of 3-alkylpyrazolines like **16a**,**b** are rare, and this strategy offers a convenient route to these novel scaffolds. A number of organotrifluoroborates (i.e., $MeBF_3K$, allyl-BF_3K) failed to provide appreciable product with this protocol, and further exploration of this cross-coupling is ongoing.

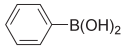
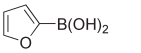
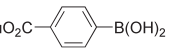
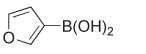
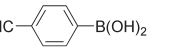
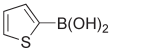
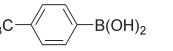
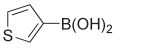
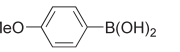
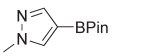
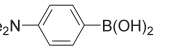
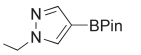
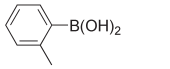
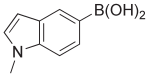
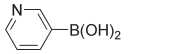
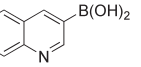
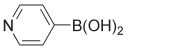
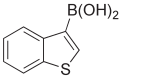
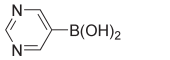
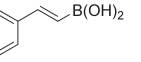
In summary, we have developed a convenient and efficient strategy for the synthesis of 3-substituted-2-pyrazolines. Exploration of the palladium-catalyzed cross-coupling chemistry of 3-sulfonyloxy-2-pyrazolines revealed that pyrazoline nonaflates are uniquely suited to undergo Suzuki cross-coupling with a variety of boronic acids and trifluoroborates. This strategy allows for the rapid, divergent incorporation of aryl, heteroaryl, and alkyl functionality into a scaffold of considerable synthetic and medicinal interest.

Experimental Section

General Procedure for Suzuki Cross-Coupling of Pyrazoline Nonaflates with Boronic Acids and Esters (Table 2 and Scheme 4). The following procedure for **15a** is representative. Nonaflate **10a** (150 mg, 0.308 mmol), 3-pyridineboronic acid (46 mg, 0.370 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (13 mg, 0.015 mmol) were combined in a microwave vial that was sealed and flushed with nitrogen (2×). Toluene (1.35 mL), EtOH (0.45 mL), and 2 M Na_2CO_3 (0.45 mL) were added, and the mixture was flushed again with nitrogen (2×). The reaction was heated to 120 °C for 10 min in the microwave. The reaction was partitioned between water and CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Silica gel chromatography (50−100% EtOAc/hexanes) afforded **15a** (74 mg, 90%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.87 (d, J = 1.9 Hz, 1H), 8.62 (dd, J = 4.8, 1.5 Hz, 1H), 8.06 (dt, J = 8.0, 1.9 Hz, 1H), 7.34 (dd, J = 8.0, 4.8 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H), 7.26−7.14 (m, 3H), 5.59 (dd, J = 11.9, 4.7 Hz, 1H), 3.74 (dd, J = 17.7, 12.0 Hz, 1H), 3.14 (dd, J = 17.7, 4.8 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 169.1, 151.3, 151.2, 148.1, 141.7, 133.7, 129.2, 128.0, 127.7, 125.7, 123.8, 60.2, 42.2, 22.2; HRMS (ESI) calcd for $C_{16}H_{16}N_3O$ $[M+H]^+$ 266.1288, found 266.1248.

TABLE 2. Boronic Acid Scope of Suzuki Cross-Coupling



entry		RB(OR')$_2$	yield (%)	entry		RB(OR')$_2$	yield (%)
1	**14b**		92	11	**14k**		91
2	**14c**		95	12	**14l**		93
3	**14d**		93	13	**14m**		95
4	**14e**		96	14	**14n**		96
5	**14f**		93	15	**14o**		82
6	**14g**		97	16	**14p**		86
7	**14h**		83	17	**14q**		95
8	**14a**		90	18	**14r**		90
9	**14i**		83	19	**14s**		91
10	**14j**		78	20	**14t**		94

General Procedure for Cross-Coupling of 10a with Potassium Organotrifluoroborates (Scheme 5). The following procedure for **16c** is representative. Nonaflate **10a** (150 mg, 0.308 mmol), potassium p-tolyltrifluoroborate (73 mg, 0.370 mmol), K_2CO_3 (128 mg, 0.925 mmol), LiCl (39 mg, 0.925 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (23 mg, 0.028 mmol) were combined in a vial that was sealed with a septum and flushed with nitrogen (2×). Toluene (1.2 mL) and water (0.40 mL) were added, and the reaction was stirred at 100 °C overnight. The mixture was cooled to room temperature and partitioned between water and CH_2Cl_2 (2×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Silica gel chromatography (0−50% EtOAc/ hexanes) provided **16c** (75 mg, 87%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.62 (d, J = 8.2 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.26−7.17 (m, 5H), 5.57 (dd, J = 11.8, 4.4 Hz, 1H), 3.71 (dd, J = 17.6, 11.8 Hz, 1H), 3.13 (dd, J = 17.6, 4.5 Hz, 1H), 2.41 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 169.0, 154.1, 142.2, 140.9, 129.7, 129.1, 128.9, 127.8, 126.8, 125.8, 60.0, 42.6, 22.2, 21.7; HRMS (ESI) calcd for $C_{18}H_{19}N_2O$ $[M+H]^+$ 279.1492, found 279.1457.

Acknowledgment. We thank Adam Beard for HRMS analysis of all compounds.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(31) By comparison, coupling of triflate **9a** with $PhCH_2BF_3K$ under the same conditions afforded only a 45% yield of **13a**.

(32) Conditions previously reported for the cross-coupling of potassium 3-trifluoroboratopropionate *tert*-butyl ester with aryl halides failed when applied to **10a**: Molander, G. A.; Petrillo, D. E. *Org. Lett.* **2008**, *10*, 1795.