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Functionalized Chromans and Isochromans via a Diastereoselective Pd(0)-Catalyzed Carboiodination

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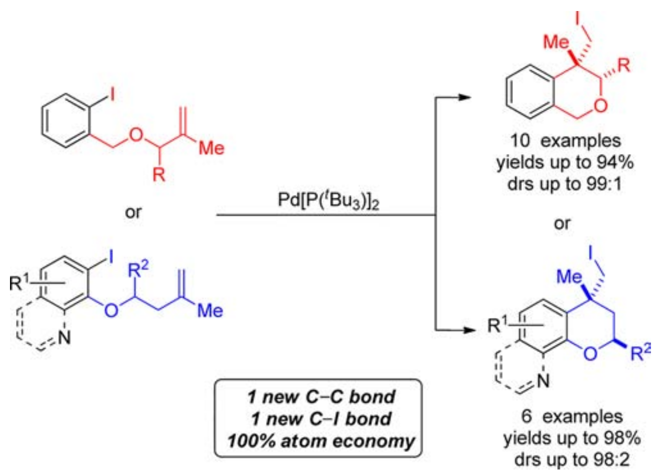
ABSTRACT



A diastereoselective approach to isochromans and chromans via Pd(0)-catalyzed carboiodination is reported. The transformations using this methodology display excellent yields and diastereoselectivities as well as broad functional group compatibility. The selectivity observed in these cyclizations, forming isochroman or chroman targets, is postulated to originate from the minimization of $A^{1,2}$ strain and axial−axial interactions, respectively. This method has also been used to highlight the concept of reversible oxidative addition to carbon−iodine bonds in polyiodinated substrates.

Heterocycles appear in numerous bioactive compounds and important synthetic intermediates.[1] The continued development of efficient strategies which allow the synthesis of these heterocyclic frameworks is of great importance to the synthetic community.[2] Transition-metal catalyzed methods resulting in newly formed carbon−carbon bonds have emerged as an effective strategy toward this end.[3] Furthermore, there is a continuing need for the development of atom-economical variants of organometallic transformations that result in the retention of important functionality within a molecule. Our group[4a−c] and others[4d,e] are interested in using Pd(0)-catalyzed carbohalogenation[5] as an efficient and atom-economical[6] synthetic strategy toward complex ring systems. Recently, we reported a Pd(0)-catalyzed bromide to iodide exchange reaction which was incorporated within various domino cyclizations.[7] These

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reactions afforded a diverse set of complex polycyclic products in good yields with moderate to excellent levels of diastereocontrol. We were interested in exploring levels of diastereocontrol in this reaction for the synthesis of chroman and isochroman motifs, as their derivatives display interesting biological and medicinal activity.[8]

Recent synthetic strategies toward their synthesis include the use of Lewis acids,[9] organocatalysis,[10] and palladium catalysis,[11] among others.[12] Despite these methods affording noteworthy reactivity and stereoselectivity, there is a lack of general and unified approaches toward both these heterocyclic skeletons.[13] We envisioned utilizing our palladium catalyzed carboiodination reaction as an integrated approach to access both of these molecular frameworks. Herein, we report the synthesis of various functionalized chromans and isochromans via a highly diastereoselective intramolecular Pd(0)-catalyzed carboiodination of alkenyl aryl iodides.

Our investigation began by analyzing the effectiveness of various bulky phosphine-containing Pd(0) precatalysts on the intramolecular cyclization of **1a** (Table 1). In accordance with previous reports,[6b,7] both Pd[(PCy$_3$)]$_2$ (entry 1) and Pd[P(*o*-tol)$_3$]$_2$ (entry 2) gave no desired isochroman product. The more bulky ligand[14] P^{t}Bu$_2$Ph only afforded trace conversion to the desired product **2a** (entry 3) despite performing moderately well in previous systems. Q-Phos was much better, affording 62% of the desired product with a diastereomeric ratio of 90:10 (entry 4). When 5 mol % P^{t}Bu$_3$[15] was employed, both yield and diastereoselectivity increased to 94% and 94:6, respectively (entry 5). In the absence of NEt$_3$ we noticed a significant decrease in yield (47%) but no decrease in stereoselectivity (entry 6). Decreasing the catalyst loading to 2.5 mol % caused a marked decrease in overall yield (77%, entry 7). The optimal reaction conditions were found to be 5.0 mol % Pd[(P^{t}Bu$_3$)]$_2$, 1 equiv of NEt$_3$ in toluene at 110 °C. The requirement of an amine base is postulated to assist the regeneration of Pd(0) from Pd(II)HX, which may result from trace intermolecular Mizoroki-Heck type processes.

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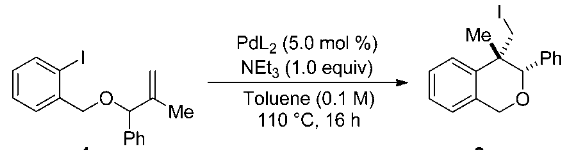
Table 1. Reaction Optimization

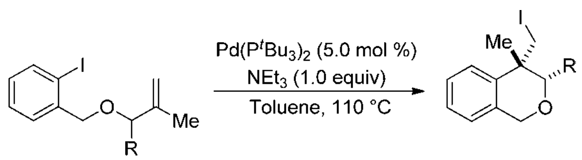


1a **2a**

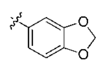
L	mol % PdL$_2$	yield (%)^{a,b}	dr (*cis/trans*)^c
P(*o*-tol)$_3$	5.0	0	–
PCy$_3$	5.0	0	–
P^{t}Bu$_2$Ph	5.0	<5	–
QPhos	5.0	62	90:10
P^{t}Bu$_3$	**5.0**	**94**^{d}	**94:6**
P^{t}Bu$_3$^{e}	5.0	47(53)	94:6
P^{t}Bu$_3$	2.5	77(23)	91:9

^{a} Calculated by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. ^{b} Value in brackets represents yield of unreacted starting material. ^{c} Calculated by ^{1}H NMR analysis of the crude reaction mixture. ^{d} Isolated yield. ^{e} Reaction run in the absence of NEt$_3$.

Table 2. Scope of Isochroman Synthesis^a



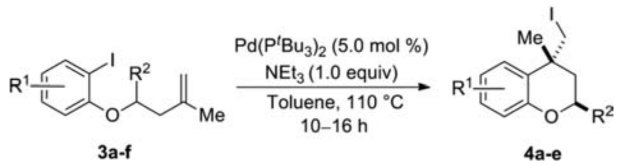
1a-j **2a-j**

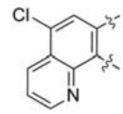
entry	R	2	yield (%)^b	dr (cis:trans)^c
1^d	Ph	**2a**	94(86)^e	94:6
2^d		**2b**	91	96:4
3^f	2-furyl	**2c**	85	92:8
4^f	2-thiophenyl	**2d**	94	91:9
5	2-pyridyl	**2e**	NR	-
6	3-pyridyl	**2f**	35	98:2
7	Cy	**2g**	81	91:9
8	Cyclopropyl	**2h**	93	90:10
9	*n*-Pr	**2i**	86	89:11
10^d	*o*-CF$_3$C$_6$H$_4$	**2j**	88	>99:1

^{a} Reaction conditions: Aryl iodide (0.2 mmol, 0.05 M), NEt$_3$ (0.2 mmol) Pd(P^{t}Bu$_3$)$_2$ (5 mol %), toluene. ^{b} Isolated yield. ^{c} dr calculated by ^{1}H NMR analysis of the crude reaction mixtures. ^{d} Reaction run at 0.1 M with respect to the aryl iodide. ^{e} Yield obtained when 100 mol % of pyridine was added to the reaction mixture. ^{f} 1.0 equiv of ^{i}Pr$_2$NEt was used instead of NEt$_3$.

A diverse set of substituted alkenyl aryl iodides were subjected to the reaction conditions to test the scope and selectivity of this transformation (Table 2). When the cyclization of **1a** was conducted on a 2 mmol scale, the

Table 3. Scope of Chroman Synthesis[a]



entry	R^1	R^2	4	yield (%)[b]	dr (*cis:trans*)[c]
1	H	Ph	**4a**	81	7:93
2	H	1-nap	**4b**	96	1:99
3		Ph	**4c**	92	10:90
4	2-OMe, 4-CHO	Ph	**4d**	86	8:92
5	4-CO_2Me	Ph	**4e**	98	9:91

[a] Reaction conditions: Aryl iodide (0.2 mmol, 0.1 M), NEt_3 (0.2 mmol), Pd(P^{t}Bu$_3$)$_2$ (5 mol %), toluene. [b] Isolated yield. [c] Calculated by ^{1}H NMR analysis of the crude reaction mixtures.

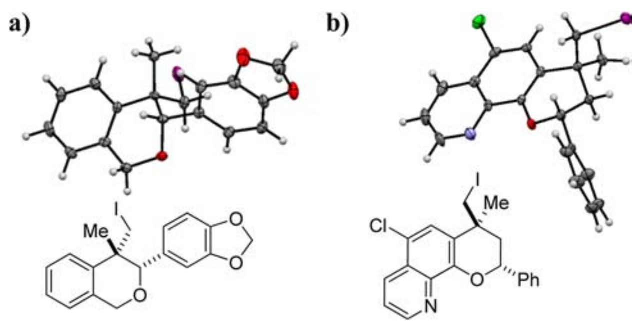


Figure 1. X-ray structures of **2b** and **4c**.

corresponding isochroman was afforded in 88% yield with no erosion of diastereoselectivity. Benzodioxole substituted **2b** was afforded in 91% yield with 96:4 diastereoselectivity. The *cis* isomer was unambiguously identified as the major product by X-ray crystallographic analysis (Figure 1a). This stereoselectivity of isochroman formation is thought to arise from the decreased $A^{1,2}$ strain[16] of the tether substituent and the vinylic CH_3 prior to carbopalladation (Scheme 1a).

Heterocyclic substituents were tolerated affording the desired isochromans **2c** and **2d** in 85% and 94% yields with 92:8 and 91:9 diastereoselectivity, respectively. 3-Pyridyl substituted **2f** was obtained in 35% yield with 98:2 diastereoselectivity. However, the 2-pyridyl analog did not undergo the desired transformation, providing only recovered starting material. Cyclohexyl containing **2g** was isolated in

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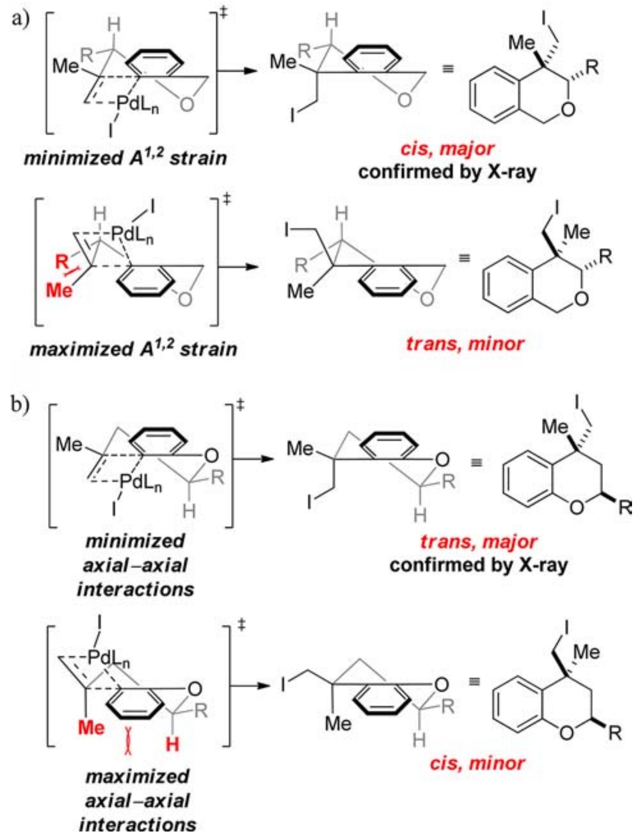
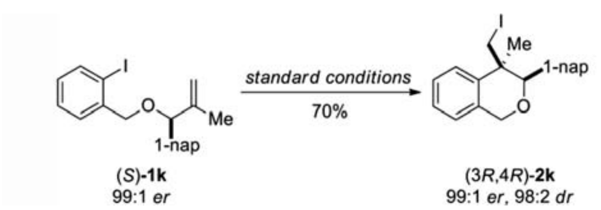
Scheme 1. Stereochemical Models Describing the Diastereoselective Carbopalladation Step for (a) Isochroman and (b) Chroman Formation



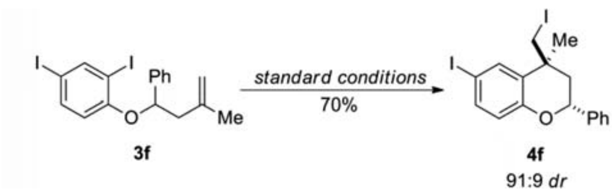
81% yield and 91:9 diastereoselectivity, while cyclopropyl **2h** and *n*-propyl-containing **2i** analogs were obtained with yields of 93% and 86% and diastereoselectivities of 90:10 and 89:11, respectively. This general trend of stereoselectivity is dependent on overall steric factors in order to obtain high levels of diastereoselectivity. As evidence of these steric requirements, *o*-CF_3 functionalized **2j** was obtained in 88% yield as a single observable diastereomer. It is noteworthy that an enantiomerically enriched precursor (*S*)-**1k** was prepared and cyclized to the corresponding isochroman (3*R*,4*R*)-**2k** with high levels of diastereoselectivity and no apparent erosion of enantiomeric excess (eq 1).



(1)

This methodology was further applied to the synthesis of substituted chromans (Table 3). 2-Phenyl chroman **4a** was obtained in 81% yield and 93:7 diastereoselectivity (entry 1). A 1-napthalene analog **4b** was afforded in 96% yield as a single diastereomer (entry 2). Notably, a switch in stereochemistry occurs from *cis* to *trans* with respect to the isochroman variants, and this stereochemical outcome was unambiguously determined through X-ray analysis (Figure 1b). The observed stereoselectivity is thought to originate from the minimization of axial−axial interactions in the carbopalladation step (Scheme 1). This reaction is exceptionally tolerant toward heteroatoms, halogens, and electron-withdrawing groups, as the desired chromans were obtained with excellent yields and diastereoselectivities (**4c**−**e**).

Remarkably, di-iodinated substrate **3f** was converted to the corresponding chroman **4f** in 70% yield and 91:9 diastereoselectivity without deleterious byproduct formation (eq 2). This result is consistent with an earlier report that highlights the possibility of reversible oxidative addition to C−I bonds by the Pd-catalyst, since it might be anticipated that the 4-iodo would react before the more hindered 2-iodo group.[4a]



(2)

In conclusion, we have developed a common approach for the diastereoselective synthesis of isochroman and chroman frameworks via a Pd(0)-catalyzed carboiodination. These transformations display generally good to excellent yields and high diastereoselectivities and have broad functional group compatibility. The stereochemistry observed in these cyclizations is postulated to originate from the minimization of $A^{1,2}$ strain and axial−axial interactions. A stereochemical model has been presented. Studies to further understand the involvement of an amine base, as well as computational analyses to explore the energetics of these cyclizations, are currently underway in our laboratory and will be reported in due course.

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

The authors declare no competing financial interest.