Functionalization of Piperidine Derivatives for the Site Selective and Stereoselective Synthesis of Positional Analogs of Methylphenidate

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Abstract: Rhodium-catalyzed C–H insertions and cyclopropanations of donor/acceptor carbenes have been used for the synthesis of positional analogs of methylphenidate. The site selectivity is controlled by the catalyst and the amine protecting group. C–H functionalization of N-Boc-piperidine using Rh_2(*R*-TCPTAD)$_4$, or N-brosyl-piperidine using Rh_2(*R*-TPPTTL)$_4$ generated 2-substitited analogs. In contrast, when *N*-α-oxoarylacetyl-piperidines were used in combination with Rh_2(*S*-2-Cl-5-BrTPCP)$_4$, the C–H functionalization produced 4-susbstiuted analogs. Finally, the 3-substituted analogs were prepared indirectly by cyclopropanation of *N*-Boc-tetrahydropyridine followed by reductive regio- and stereoselective ring-opening of the cyclopropanes.

The piperidine ring with substituents at different positions is a prominent structural element in numerous pharmaceuticals,[1] including Ritalin (methylphenidate), a therapeutic agent for attention deficit hyperactivity disorder.[2] Traditional synthetic routes to these heterocycles typically involve ring construction or require functionalized piperidines,[2-3] with the latter being challenging owing to the lack of readily available enantiopure piperidine precursors. An alternative strategy would be the direct, site selective C–H functionalization, ideally at any position of the piperidine moiety at will. Many examples have been disclosed on the use of C–H functionalization as a key disconnection strategy for the synthesis of natural products and pharmaceutical targets.[4] The majority of these applications rely on using either directing groups[5] in the substrate or on the inherent reactivity[6] of the substrate to control site selectivity. Considerable interest has also been shown in developing catalyst-controlled[7] or enzyme controlled[8] C–H functionalization reactions. The C–H functionalization at the C2 position on piperidine derivatives has been achieved using several different approaches.[9] However, selective functionalization at the remote positions of the piperidine moiety, i.e. C3 and C4, is limited.[10-11]

We have been exploring the rhodium-catalyzed reactions of donor/acceptor carbenes for catalyst-controlled C–H functionalization.[7e,f] Recently, we have designed catalysts that are capable of selective functionalization of unactivated primary, secondary and tertiary C–H bonds,[12] unactivated C–H bonds over electronically activated C–H bonds,[13] and desymmetrization of alkylcyclohexanes.[14] In this project, we describe the application of these catalysts to generate methylphenidate analogs with substituents at either C2, C3 or C4 of the piperidine rings starting from appropriate piperidine derivatives (Figure 1). The C–H functionalization at C2 is electronically preferred, because the build-up of positive charge at carbon during the C–H functionalization would be stabilized by the nitrogen group.[15,16] The C–H bond at C3 would be deactivated through the inductive effect of nitrogen. The electronic deactivation would be less for C4, which should be sterically the most accessible position. Thus, a direct functionalization of the C–H bond at C4 should be feasible by sterically shielding at C2 position, while we envisioned that C–H activation at C3 might become possible by an indirect approach via regioselective ring-opening of an appropriate cyclopropanated tetrahydropyridine.

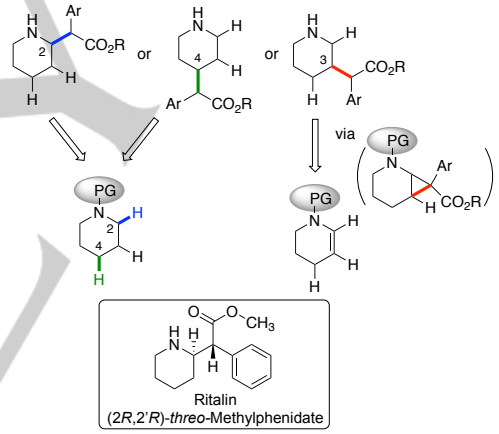

Figure 1. Synthetic strategies towards C–H functionalization of piperidines at C2, C3 and C4. C2–H: electronically activated but sterically hindered; C3-H: electronically deactivated through inductive effect of NPg, indirect approach through regio- and stereoselective cyclopropane ring-opening; C4-H: accessible if the electronic preference for C2 can be overridden by steric shielding of catalyst and NPg.

The first stage of this project was to optimize the C2 functionalization of piperidines. The basic transformation is one of the early classic C–H functionalization reactions of donor/acceptor carbenes, described independently by Davies[15] and Winkler.[16] In the original studies, the control of both the diastereoselectivity and enantioselectivity of the C–H functionalization was relatively moderate. Therefore, we decided to re-examine this transformation using the specialized chiral dirhodium catalysts that have been recently developed. The key optimization studies are summarized in Table 1 and Scheme 1 (see SI for more extensive details). The original Rh_2(*S*-DOSP)$_4$-catalyzed reaction of methyl aryldiazoacetate **2a** reacting with *N*-Boc-piperidine **1a** gives a 1:1 mixture of diastereomers.[15] Several of the newer chiral dirhodium tetracarboxylate catalysts

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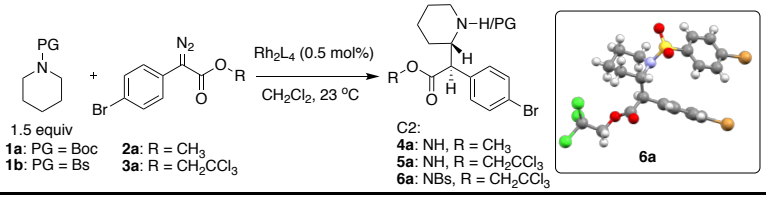
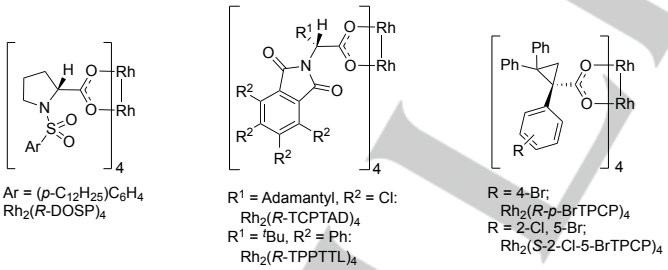
Table 1. Optimization Studies for C2 Functionalization[a]



Entry	**1** (PG)	**2a**/**3a** (R)	L	Yield[b], %	d.r.[c]	ee[d], %
1[e][f]	**1a** (Boc)	**2a** (CH_3)	*S*-DOSP	69	1.5:1	-69
2[f]	**1a** (Boc)	**2a** (CH_3)	*R*-TCPTAD	69	1.4:1	66
3[f]	**1a** (Boc)	**2a** (CH_3)	*R*-*p*-BrTPCP	41	1.2:1	27
4[f]	**1a** (Boc)	**2a** (CH_3)	*R*-TPPTTL	69	1.5:1	54
5[f]	**1a** (Boc)	**2a** (CH_3)	*S*-2-Cl-5-BrTPCP	83	5.3:1	83
6[f]	**1a** (Boc)	**3a** (CH_2CCl_3)	*S*-2-Cl-5-BrTPCP	73	3.6:1	65
7[f]	**1a (Boc)**	**3a (CH_2CCl_3)**	***R*-TCPTAD**	**83**	**11:1**	**93**
8[f]	**1a** (Boc)	**3a** (CH_2CCl_3)	*R*-TPPTTL	80	27:1	69
9	**1b (Bs)**	**3a (CH_2CCl_3)**	***R*-TPPTTL**	**76**	**>30:1**	**77**
10[g]	**1b** (Bs)	**3a** (CH_2CCl_3)	*R*-TPPTTL	87	22:1	76
11[h]	**1b** (Bs)	**3a** (CH_2CCl_3)	*R*-TPPTTL	42	26:1	72

[a] Reaction conditions: a solution of **2a-3a** (0.5 mmol) in 4 mL pentane/CH_2Cl_2 was added over 2 h to the solution of Rh_2L_4 (0.5 mol %) and **1a-b** (0.75 mmol) in 2 mL pentane/CH_2Cl_2. [b] Isolated yield. [c] Determined from crude ^{1}H NMR. [d] Determined by chiral HPLC analysis of isolated product. [e] Reaction in pentane instead of CH_2Cl_2. [f] Analysis of yield, d.r. and ee were on free amine product after Boc-deprotection via trifluoroacetic acid. [g] Reaction at refluxing CH_2Cl_2 (39 °C). [h] Reaction at 0 °C. Boc = *tert*-butyloxycarbonyl, Bs = *p*-bromo-phenylsulfonyl. The absolute stereochemistry was deduced by comparison of products to those of the earlier study[15a] and confirmed by crystal structure of **6a**.

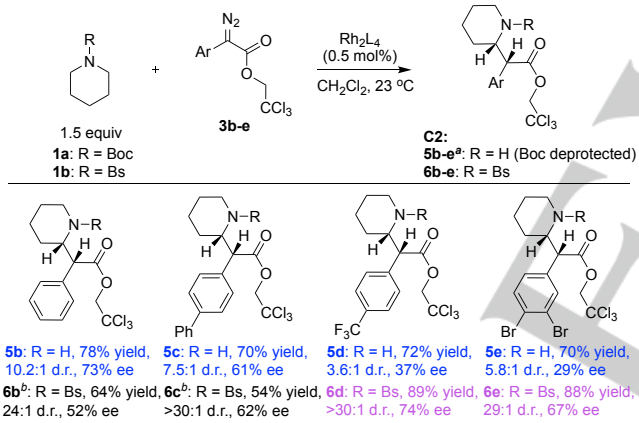


Scheme 1. Catalyst Structures.

were tested under the same reaction conditions. Most of the catalysts furnished the C2-functionalized product **4a** with 1:1 to 2:1 d.r. (entries 2-4) and low to moderate enantioselectivity (27-66% ee), whereas the C_4-symmetric catalyst, Rh_2(*S*-2-Cl-5-BrTPCP)$_4$, enhanced the stereoselectivity to 5.3:1 d.r. and 83% ee for the major diastereomer **4a** (entry 5). Another major advance in site selective C–H functionalization has been the use of aryldiazoacetates containing trichloroethyl esters instead of methyl esters as donor/acceptor carbene precursors.[17] Hence, we evaluated the influence of the ester switch on the stereoselectivity of the C2 functionalization. The level of diastereoselectivity in the reaction of **1a** using trichloroethyl derivative **3a,** catalyzed by Rh_2(*S*-2-Cl-5-BrTPCP)$_4$, dropped considerably versus the methyl ester (entry 6). Fortunately, the

Rh_2(*R*-TCPTAD)$_4$-catalyzed transformation to form **5a** lead to a considerable improvement in the stereoselectivity (11:1 d.r., 93% ee) in 83% yield (entry 7). The diastereoselectivity could be greatly improved (27:1 d.r.) when Rh_2(*R*-TPPTTL)$_4$ was used as catalyst, but with lower enantioselectivity (69% ee, entry 8). Higher enantioselectivity (77% ee) with Rh_2(*R*-TPPTTL)$_4$ was obtained when an arylsulfonyl piperidine derivative **1b** was used (**6a**, entry 9). Further optimization on temperature showed improvement on yield with small decrease in stereoselectivity at higher temperature (39 °C: 87% yield, 22:1 d.r., 76% ee, entry 10), while 0 °C caused decline in both yield and stereoselectivity (entry 11).

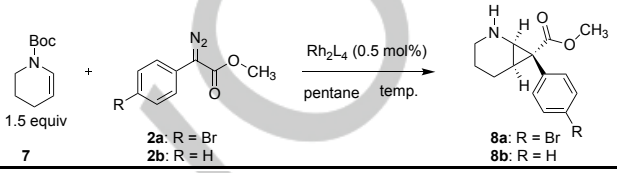
The scope of the C2 functionalization of piperidine was examined using the two most promising conditions, *N*-Boc-piperidine functionalization catalyzed by Rh_2(*R*-TCPTAD)$_4$ and *N*-Bs-piperidine functionalization catalyzed by Rh_2(*R*-TPPTTL)$_4$ (Scheme 2). The Rh_2(*R*-TCPTAD)$_4$-catalyzed reactions gave moderate yield but variable stereoselectivity, reaching low levels with electron deficient aryldiazoacetates. In contrast, the Rh_2(*R*-TPPTTL)$_4$-catalyzed reactions were highly diastereoselective for all the substrates (29->30:1 d.r.) and maintained relatively constant levels of enantioselectivity (52-73% ee).



Scheme 2. Substrate Scope of C2 Functionalization. The *N*-Boc-piperidine (**1a**) functionalization was catalyzed by Rh_2(*R*-TCPTAD)$_4$ to form **5b-e** and *N*-Bs-piperidine (**1b**) functionalization was catalyzed by Rh_2(*R*-TPPTTL)$_4$ to form **6b-e**. [a]Boc group was removed via trifluoroacetic acid treatment before analysis. [b]reaction conducted in refluxing CH_2Cl_2 (39 °C).

Having established the C2 functionalization of piperidine, we then explored how to introduce the arylacetate group at C3 position. The direct C–H functionalization of piperidines was not considered to be a viable option, because the C3 position would be deactivated towards carbene C–H insertions caused by the inductively electron-withdrawing effect of the nitrogen. Therefore, we explored an indirect approach via asymmetric cyclopropanation of a tetrahydropyridine followed by a reductive ring-opening of the cyclopropane intermediate. A catalyst screen was conducted on the cyclopropanation of the *N*-Boc-tetrahydropyridine **7** to generate **8** and the key results are shown in Table 2 (see SI for more extensive details). It is well established that Rh_2(*R*-DOSP)$_4$ performs best when the methyl ester of aryldiazoacetates and hydrocarbon solvents are used.[7e] The classic catalyst, Rh_2(*R*-DOSP)$_4$, is still unmatched for this type of cyclopropanation with methyl *p*-bromophenyldiazoacetate **2a**, while other catalysts are considerably inferior (entry 1-4). A temperature screen revealed that 0 °C was the optimum condition (entries 5-7). Under these conditions, the cyclopropanation with methyl phenyldiazoacetate **2b** proceeded in 87% yield, >30:1 d.r. and 95% ee.

Table 2. Optimization Studies for Cyclopropanation[a]



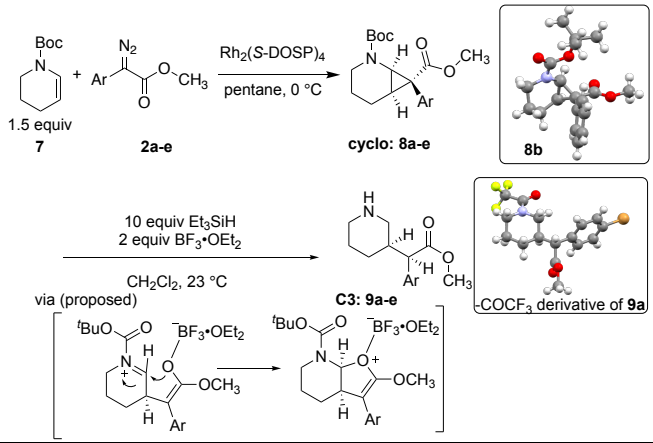
Entry	2	L	temp., °C	Yield[b], %	d.r.[c]	ee[d], %
1	**2a** (Br)	*R*-TCPTAD	23	75	>30:1	3
2	**2a** (Br)	*R*-*p*-BrTPCP	23	73	>30:1	8
3	**2a** (Br)	*S*-2-Cl-5-BrTPCP	23	77	>30:1	-69
4	**2a** (Br)	*R*-DOSP	23	76	>30:1	-89
5	**2b** (H)	*S*-DOSP	23	83	>30:1	-92
6	**2b (H)**	***S*-DOSP**	**0**	**87**	**>30:1**	**95**
7	**2b** (H)	*S*-DOSP	-40	85	>30:1	95

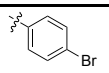
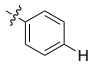
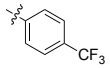
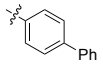
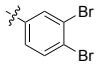
[a] Reaction conditions: a solution of **2a-e** (0.5 mmol) in 12 mL of solvent was added over 2 h to the solution of Rh_2L_4 (0.5 mol%) and **7** (0.75 mmol) in 2 mL of solvent. [b] Isolated yield. [c] Determined from crude ^{1}H NMR. [d] Determined by chiral HPLC analysis of isolated product. A negative sign indicates that the product is the opposite enantiomer to the one drawn in the scheme. Boc = *tert*-butyloxycarbonyl.

The next stage was to combine the asymmetric cyclopropanation with the reductive ring-opening. This reaction was examined with five representative examples of aryldiazoacetates, and the results are summarized in Table 3. Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation of aryldiazoacetates **2a-e** were examined and the cyclopropanes **8a-e** were produced in high yields (85-93%) as single diastereomers (>30:1 d.r.) and moderate to high levels of enantiocontrol (81-95% ee). The X-ray structure of **8b** was consistent with cyclopropanation occurring at the *Re* face of the carbene, which is standard for Rh_2(*S*-DOSP)$_4$-catalyzed reactions. Reductive ring-opening of the cyclopropanes **8a-e** using Et_3SiH and BF_3•Et_2O[18] resulting in concomitant removal of the N-Boc protecting group and the generation of the desired C3-substituted analogs **9a-e** in 67-92% yield as single diastereomers (>30:1 dr) and retention of the asymmetric induction obtained in the cyclopropanation. The absolute stereochemistry was assigned basing on the crystal structure of trifluoroacetyl-protected **9a**. The retention of the chirality at the benzylic carbon was proposed to raise from the formation of a bicyclic intermediate from the ring-opened enolate,

in which the bottom face *cis* to the bridging hydrogens is more accessible.

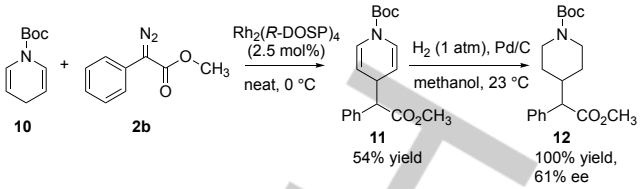
Table 3. Substrate Scope of C3 Functionalization[a]



Entry	Ar	8		9		
		yield, %	ee, %	yield, %	d.r.	ee, %
1		93 (**8a**)	92	67 (**9a**)	>30:1	93
2		87 (**8b**)	95	70 (**9b**)	>30:1	92
3		86 (**8c**)	90	92 (**9c**)	>30:1	90
4		85 (**8d**)	86	77 (**9d**)	>30:1	87
5		90 (**8e**)	81	90 (**9e**)	>30:1	80

[a] Minimal amount of $PhCF_3$ was added to dissolve the aryldiazoacetate.

Two approaches were examined to install the arylacetate functionality at the C4 position of the piperidine. The first attempt examined the allylic C–H functionalization of N-Boc-dihydropyridine **10** as the substrate (Scheme 3). Although the dihydropyridine might be expected to be susceptible to cyclopropanation rather than C–H functionalization, we had already established that 1,4-cyclohexadiene strongly favors C–H functionalization.[19] We expected the doubly allylic position in **10** to be similarly activated towards C–H functionalization, and this proved to be the case. The catalyst screen using the phenyldiazoacetate **2b** revealed that Rh_2(*R*-DOSP)$_4$ is the optimum catalyst (see SI for details). Due to the instability of the dihydropyridine **10** and the product **11**, the reaction was somewhat challenging and neat conditions were used for the C–H insertion followed by immediate hydrogenation of **11**. Under these conditions, the C4-substituted product **12** was obtained in 54% overall yields and 61% ee.

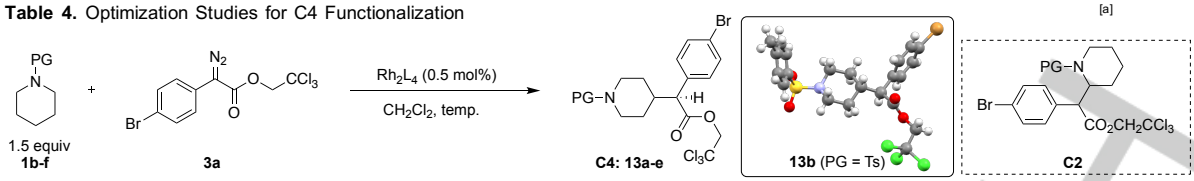


Scheme 3. C4 Analog from N-Boc-dihydropyridine.

A more innovative approach to C4 substituted analogs would be the direct C–H functionalization on the saturated piperidine derivative. We have already proven that the rhodium-stabilized donor/acceptor carbenes are sterically demanding and some of the new catalysts drive the site selectivity away from the electronically favored sites to the sterically most accessible sites. Therefore, by appropriate choice of catalyst and protecting group on nitrogen, we anticipated that it should be possible to alter the selectivity from C2 to C4 positions. The optimization study to achieve this goal is shown in Table 4. In the initial examination of the catalysts in reactions on N-*p*-bromophenylsulfonyl-piperidine, most of the catalysts gave clean C2-functionalization selectivity or no reaction (entries 1-3), while the Rh_2(*S*-2-Cl-5-BrTPCP)$_4$-catalyzed reaction (entry 5) proceeded with 4.2:1 r.r. favoring the C4 insertion product **13b** in good yield (67%) and enantiocontrol (90% ee). As expected, C2 position is less activated with electron-withdrawing substituent on the arylsulfonyl group and gave slightly improvement on the site selectivity (entry 6 vs, entry 5 and 4). Less bulky protecting group was believed to have negative effect on the steric blocking of C2 position, however, the smaller mesyl group caused increased ratio of C4 product (entry 7 vs. entry 4). With limited effect on the site selectivity with various sulfonyl groups, a more electron-withdrawing protecting group, α-oxoarylacetyl group as in **1f**, was utilized for better selectivity. With this adjustment, the site selectivity between C4 and C2 improved to >30:1 r.r. and **13e** was formed in 98% ee, preferring the *S* configuration at the benzylic chiral center according to the crystal structure of **13b**. Alternation of the temperature and substrates ratio enhanced the yield (50% at 23 °C and 1.5:1 **1f**:**3a**, entry 9 vs. 61% at 39 °C and 1:1.5 **1f**:**3a**, entry 11) without influence on site and enantioselectivity. The efficiency of Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ in C-4 functionalization of **1f** was explored using the optimized conditions (Scheme 4). When the substituents on the aryl ring in the diazoacetates were electronic-withdrawing (**13f, 13h**) high enantiocontrols were retained (96-98% ee) with moderate yields (50-57%). When electron-rich aryl ring in the diazoacetate was used, both yield and enantioselectivity decrease (19% yield, 75% ee for **13g**).

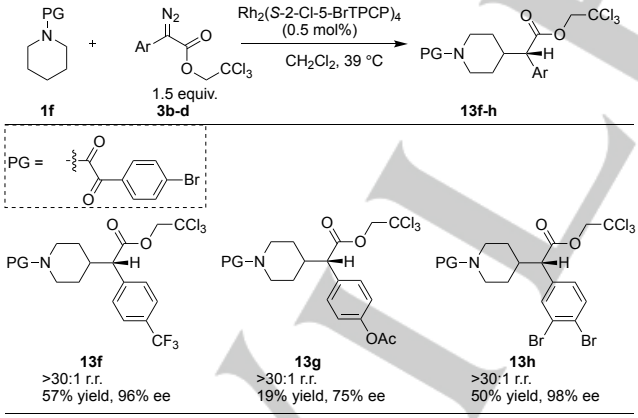
In summary, this study reveals that by appropriate considerations of the electronic and steric demands of the dirhodium catalysts, it is possible to functionalization piperidines at C2, C3 or C4. This leads to the synthesis of a small library of position analogs of methylphenidate.

Table 4. Optimization Studies for C4 Functionalization



Entry	1	PG	L	temp., %	r.r. (**C4**:**C2**)[b]	yield(**C4**)[c], %	ee (**C4**)[d], %
1	**1b**		*R*-DOSP	23	<1:30	--	--
2	**1b**		*R*-TCPTAD	23	<1:30	--	--
3	**1b**	O_2S–Br	*R*-*p*-BrTPCP	23	--[e]	--	--
4	**1b**		*S*-2-Cl-5-BrTPCP	23	4.2:1	76 (**13a**)	90
5	**1c**	O_2S–CH_3	*S*-2-Cl-5-BrTPCP	23	4.0:1	30[f] (**13b**)	96
6	**1d**	O_2S–CF_3	*S*-2-Cl-5-BrTPCP	23	4.7:1	65 (**13c**)	96
7	**1e**	O_2S–CH_3	*S*-2-Cl-5-BrTPCP	23	5.6:1	78 (**13d**)	97
8	**1f**	O, O, Br	*S*-2-Cl-5-BrTPCP	23	>30:1	50 (**13e**)	97
9	**1f**	O, O, Br	*S*-2-Cl-5-BrTPCP	39	>30:1	76 (**13e**)	97
10[g]	**1f**	O, O, Br	***S*-2-Cl-5-BrTPCP**	**39**	**>30:1**	**76 (13e)**	**97**

[a] Reaction conditions: a solution of **2b** (0.5 mmol) in 4 mL CH_2Cl_2 was added over 2 h to the solution of Rh_2L_4 (0.5 mol%) and **1b-f** (0.75 mmol) in 2 mL CH_2Cl_2. The reaction was allowed to stir for overnight. [b] Determined by crude ^{1}H-NMR. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] No C–H functionalization products. [f] 40% yield of primary C–H insertion on tosyl group. [g] 1.5 equiv. of **3a** and 1.0 equiv. of **1f** were used.



Scheme 4. Substrate Scope of C4 Functionalization.

Acknowledgements

We thank Dr. John Bacsa for the X-ray structure determination. Financial support (HMLD) was provided by NSF under the CCI Center for Selective C–H Functionalization (CHE-1700982) and AbbVie. Financial support (OR) was provided by Elitenetzwerk Bayern (SYNCAT). Finacial support for the development of the catalyst, Rh_2(*R*-TPPTTL)$_4$ was provided by NIH (GM099142-05). We thank Dr. Eric A. Voight and Mark A. Matulenko from AbbVie, and Shane W. Krska and Jaume Balsells-Padros from Merck for helpful discussions. Funds to purchase the NMR and X-ray spectrometers used in these studies were supported by NSF (CHE 1531620 and CHE 1626172).

Keywords: C–H functionalization • rhodium • piperidines • regioselectivity • diastereoselectivity

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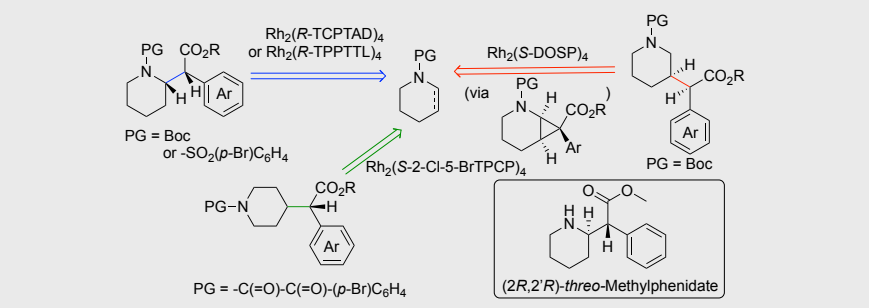

Regio, diastereo- and enantioselective C-2, C-3 and C-4 functionalization on piperidine ring controlled by catalysts and protecting groups.

Wenbin Liu, Tobias Babl, Alexander Röther, Oliver Reiser and Huw M. L. Davies**

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Functionalization of Piperidine Derivatives for the Site Selective and Stereoselective Synthesis of Positional Analogs of Methylphenidate