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Highly Diastereoselective Arylations of Substituted Piperidines

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Supporting Information

ABSTRACT: A highly diastereoselective methodology for the preparation of various substituted piperidines via Negishi cross-couplings with (hetero)aryl iodides was developed. Depending on the position of the C−Zn bond relative to the nitrogen (position 2 vs position 4), the stereoselectivity of the coupling can be directed toward either the trans- or cis-2,4-disubstituted products. Density functional theory calculations on the relative stabilities of the Zn and Pd intermediates were performed to explain the high diastereoselectivities obtained. A novel 1,2-migration of Pd further expands this method to the stereoselective preparation of 5-aryl-2,5-disubstituted piperidines.

Substituted piperidines are ubiquitous structural motifs present in numerous bioactive alkaloids.[1] In order to ensure appropriate biological activity, many of them have to be prepared in a stereodefined manner.[1] Therefore, the development of efficient methods for the diastereoselective construction of piperidines bearing more than one stereocenter represents an important synthetic task.[2] Still, procedures for the direct diastereoselective arylation of the piperidine ring are scarce.[3] Only one isolated example, involving the diastereoselective coupling of a 6-methylpiperidin-2-yl organometallic with 4-bromoveratrole to furnish the trans-2,6-disubstituted product, has been reported.[3c] To date, the direct stereoselective synthesis of 2,4- and 2,5-disubstituted arylated piperidines via $C(sp^3)-C(sp^2)$ cross-coupling remains a challenging problem. We recently developed highly diastereoselective couplings of several substituted cycloalkyl derivatives mediated by Pd.[4] Herein we report that Pd-catalyzed cross-couplings can be efficiently used for a highly diastereoselective preparation of various disubstituted or annulated piperidines.

We previously showed that cross-couplings of substituted cyclohexylzinc reagents with diverse aryl halides result in the stereoconvergent formation of the thermodynamically favored arylpalladium intermediates, which upon reductive elimination afford the desired arylated products with retention of configuration (d.r. up to >99:1).[4] Because of the structural importance of piperidines, we envisioned performing diastereoselective cross-couplings with the related substituted piperidinylzinc compounds. By exploiting the pseudo-allylic strain induced by the protecting group on N,[5] we were able to prepare both the cis- and trans-2,4-disubstituted piperidine derivatives with excellent diastereoselectivity.

First, we generated various piperidin-2-ylzinc reagents of type **1** starting from the respective piperidines **2a**−**e** according to the procedures of Beak and Lee[6] and Coldham and Leonori.[3c] To our delight, the Pd-catalyzed cross-coupling of **1a**−**e** with various aryl and heteroaryl iodides using 2% SPhos[7] or 5% RuPhos[8] and 2−5% $Pd(dba)_2$ as the catalyst system furnished the desired α-arylated products **3** in 54−84% yield with an exceptional level of diastereoselectivity (d.r. of 95:5 to >99:1) (Table 1). Thus, cross-coupling of the 4-methyl-substituted piperidinylzinc reagent **1a** with electron-rich 4-iodoanisole using 2% $Pd(dba)_2$ and 2% SPhos at 55 °C furnished exclusively the cis-configured product **3a** in 78% yield (entry 1 of Table 1).[9]

Coupling of **1a** with electron-poor aryl iodides and 4-iodopyridine under the same conditions gave the products **3b**−**f** with d.r. from 95:5 to 98:2 (entries 2−6). Under slightly altered conditions (5% $Pd(dba)_2$ and 5% RuPhos at 55 °C), the piperidinylzinc reagent **1b** bearing a large phenyl ring instead of the smaller methyl substituent provided the cis products **3g**−**i** with comparable yields (64−79%) and equally high diastereoselectivities (97:3 to >99:1) (entries 7−9). Even the functionalized piperidinylzinc reagent **1c** bearing an OSi(*i*-Pr)$_3$ (OTIPS) group at position 4 reacted smoothly, furnishing the cis α-arylated products **3j**−**m** in high yields (81−84%) with d.r. between 95:5 and 97:3 (entries 10−13). The method also proved applicable to the *trans*-decahydroisoquinolinyl scaffold. By using the method of Beak and Lee,[6] we were able for the first time to metalate this heterocycle regioselectively at position 3. Cross-coupling of the resulting organozinc species **1d** led to the stereodefined 2,4,5-trisubstituted products **3n**−**p** in 54−69% yield with excellent d.r. (97:3 to >99:1) (entries 14−16). In the case of the 5-methyl-substituted reagent **1e**, lower temperatures were necessary in order to achieve high diastereoselectivities (Table 1). Thus, the trans-2,5-disubstituted products **3q**−**r** were obtained in moderate yields of 59−62% with a high d.r. of 95:5 (entries 17 and 18).

Complementary to the diastereoselective preparation of the cis-2,4-disubstituted piperidines, we also report the synthesis of the corresponding trans isomers by switching the positions of the substituent and the C−Zn bond. Thus, in preliminary experiments, we prepared the 2-substituted piperidin-4-ylzinc reagent **4a** via LiCl-promoted Zn insertion into iodide **5a**[10] and subjected it to cross-coupling with 4-iodobenzonitrile and iodobenzene using 5% $TMPP_2PdCl_2$[11] as the catalyst (Table 2).[4] The trans coupling products **6a** and **6b** were obtained in 50−74% yield with d.r. of 91:9 and 92:8, respectively (entries 1 and 2 of Table 2).[12] By examining the NMR spectra of **6a** and **6b**, we found that both revealed the presence of two Boc conformers at room temperature. These

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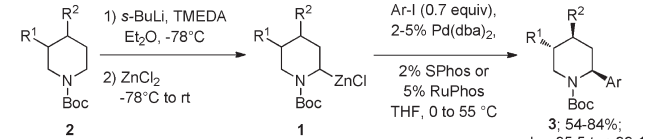
Table 1. Diastereoselective Cross-Coupling of Substituted Piperidin-2-ylzinc Reagents



2
2a: R^1=H; R^2=Me
2b: R^1=H; R^2=Ph
2c: R^1=H; R^2=OTIPS
2d: R^1=R^2=*trans*-$(CH_2)_4$-
2e: R^1=Me; R^2=H

1
1a: R^1=H; R^2=Me
1b: R^1=H; R^2=Ph
1c: R^1=H; R^2=OTIPS
1d: R^1=R^2=*trans*-$(CH_2)_4$-
1e: R^1=Me; R^2=H

3; 54-84%; d.r.: 95:5 to >99:1

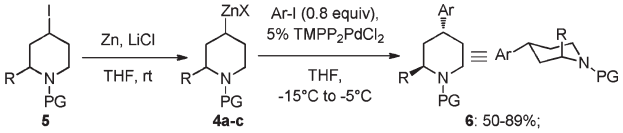
entry	product	yield (%)[a]	d.r.[b]
1	**3a**: Ar: 4-MeO-C_6H_4	78	>99:1[c]
2	**3b**: Ar: 4-F_3C-C_6H_4	81	95:5[c]
3	**3c**: Ar: 3-Cl-C_6H_4	76	96:4[c]
4	**3d**: Ar: 3-NC-C_6H_4	64	97:3[c]
5	**3e**: Ar: 4-EtO_2C-C_6H_4	67	98:2[c]
6	**3f**: Ar: 4-pyridinyl	73	95:5[c]
7	**3g**: Ar: 4-F_3C-C_6H_4	64	97:3[d]
8	**3h**: Ar: 4-NC-C_6H_4	79	>99:1[d]
9	**3i**: Ar: 4-MeO_2C-C_6H_4	67	99:1[d]
10	**3j**: Ar: 4-EtO_2C-C_6H_4	84	97:3[e]
11	**3k**: Ar: 4-F-C_6H_4	83	95:5[e]
12	**3l**: Ar: 4-F_3C-C_6H_4	81	95:5[e]
13	**3m**: Ar: 4-NC-C_6H_4	81	97:3[e]
14	**3n**: Ar: 4-F_3C-C_6H_4	69	>99:1[d]
15	**3o**: Ar: 4-NC-C_6H_4	54	>99:1[d]
16	**3p**: Ar: 4-MeO-C_6H_4	60	97:3[d]
17	**3q**: Ar: 4-NC-C_6H_4	62	96:4[f]
18	**3r**: Ar: 4-EtO_2C-C_6H_4	59	95:5[f]

[a] Isolated yield. [b] Determined by GC and/or $^1H/^{13}C$ NMR analysis. [c] 2% $Pd(dba)_2$, 2% SPhos, THF, 55 °C, 12 h. [d] 5% $Pd(dba)_2$, 5% RuPhos, THF, 55 °C, 12 h. [e] 5% $Pd(dba)_2$, 5% RuPhos, THF, 55 °C, 60 h. [f] 5% $Pd(dba)_2$, 5% RuPhos, THF, 0 °C (6 h), then rt (12 h), then 40 °C (12 h).

findings were supported by DFT analysis.[13] Furthermore, the X-ray structures of the previously prepared *N*-Boc-protected piperidines **3d** and **3h**[9] (entries 6 and 8 of Table 1) showed a twisted ring conformation, whereas the structures of the *N*-Ts-protected piperidines **3na** and **3qa**[9] displayed an almost perfect chairlike structure. Thus, we prepared the corresponding N-tosylated zinc reagent **4b**. Cross-coupling of **4b** with 4-iodobenzonitrile under the same reaction conditions led to the *exclusive formation* of the trans isomer **6c** in 70% yield (entry 3). Remarkably, the couplings of the zinc reagent **4c** bearing only a small methyl group in position 2 also gave the corresponding trans isomers **6e** and **6f** with excellent diastereoselectivity (d.r. = 97:3; entries 5 and 6).

In order to explain the distinct stereochemical outcomes of these couplings, the cis/trans stability differences between **3g** and

Table 2. Diastereoselective Cross-Coupling of 2-Substituted Piperidin-4-ylzinc Reagents



5
5a: PG= Boc; R= 4-F_3C-C_6H_4
5b: PG= Ts; R= 4-F_3C-C_6H_4
5c: PG= Ts; R= Me

4a-c X=Cl,I

6: 50-89%; d.r.: 91:9 to >99:1

entry	product	yield (%)[a]	d.r.[b]
1	**6a**: Ar: 4-NC-C_6H_4	74	91:9
2	**6b**: Ar: Ph	50	92:8
3	**6c**: Ar: 4-NC-C_6H_4	70	>99:1
4	**6d**: Ar: 4-MeO_2C-C_6H_4	69	96:4
5	**6e**: Ar: 4-NC-C_6H_4	84	97:3
6	**6f**: Ar: 4-MeO_2C-C_6H_4	89	97:3

[a] Isolated yield. [b] Determined by GC and/or $^1H/^{13}C$ NMR analysis.

6b together with the corresponding data for the Zn and Pd intermediates were analyzed at the B3LYP/631SVP level (Scheme 1 and Table 3).[14] From our former studies,[4] it was clear that the relative stabilities of the Pd intermediates represent the crucial factor for the determination of the final diastereoselectivity of the cross-coupling.

The stabilities of the products (**3g** and **6b**) and the corresponding Zn intermediates were calculated to refine our mechanistic picture. In contrast to the corresponding cyclohexanes, in which an overall equatorial substitution pattern is thermodynamically preferred,[4] the pseudo-allylic strain in *N*-Boc piperidines caused by the partial double-bond character of the amide bond forces the substituent vicinal to the nitrogen into an axial orientation.[5] Therefore, cis isomer **3g** was found to be much less stable (by 13.4 kJ/mol) than trans isomer **6b**. Detailed DFT conformational analysis (chair vs twist boat) showed that the energy difference between the chair and twist-boat conformations is negligible for **3g** but large for **6b**, confirming our observations on **6a** and **6b** by ^1H and ^{13}C NMR spectroscopy.

The stabilities of the respective Pd and Zn intermediates involved in the formation of the cross-coupling products **3g** and **6b** were calculated using the same model as in our recent study of the analogous cyclohexyl systems.[4] Whereas the diastereomeric substituted cyclohexylzinc complexes possessed very similar energies, large differences in the stabilities of the corresponding piperidinylzinc species were found. In the case of piperidin-2-ylzinc reagent **1b**, the equatorial orientation of the C−Zn bond is stabilized by its coordination to the carbonyl oxygen atom of the Boc group, leading to a pentacoordinated Zn center. This results in an energetic preference for **eq-1b** by 15.4 kJ/mol (entry 1 of Table 3). Since pseudo-allylic strain in the 4-zincated piperidinyl species **4a** dictates an axial position of the substituent at C2, the axial orientation of the C−Zn bond is hampered by 1,3-diaxial repulsions, causing **ax-4a** to be the most stable conformer (entry 2). This underlines the "Janus-like" nature of the Boc group, which shows its sterically demanding, repulsive character toward vicinal substituents yet turns into an electrostatically attractive neighbor with Lewis acidic metal centers

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Scheme 1. DFT Conformational Analysis of Cis Isomer 3g and Trans Isomer 6b

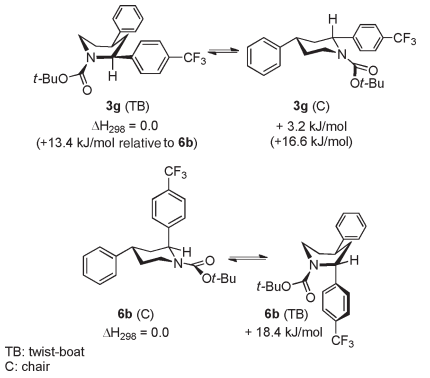
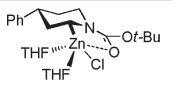
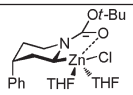
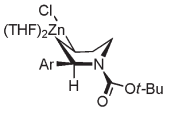
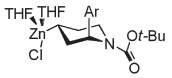
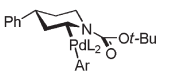
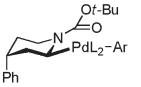
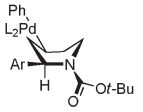
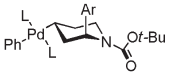


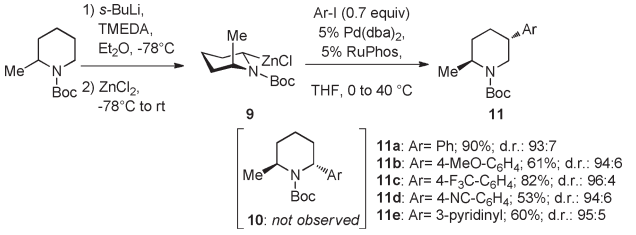
Table 3. DFT-Calculation-Based Conformational Analysis of the Diastereomeric Zinc and Palladium Complexes

entry	Zn- and Pd-intermediates [a]	$\Delta H^{298}_{ax\text{-}eq}$ (kJ/mol) [b]	
1	 **eq-1b** (C)	+15.4	 **ax-1b** (C)
2	 **eq-4a** (TB)	-8.4	 **ax-4a** (C)
3	 **eq-7** (C)	+15.0	 **ax-7** (C)
4	 **eq-8** (TB)	-8.6	 **ax-8** (C)

[a] Ar: 4-$CF_3C_6H_4$. Preferred conformations are indicated as twist-boat (TB) or chair (C). [b] Calculated energetic differences (B3LYP/631SVP) between the thermodynamically lowest conformers of the two diastereomers; L = PMe_3.

present at the same position. As in the cyclohexyl systems, the Pd moiety shows a preference for the equatorial position in all cases. In the piperidin-2-ylpalladium intermediates **eq-7** and **ax-7** (entry 3), where the square-planar coordination sphere of Pd is not perturbed, this natural preference is magnified by a close contact between the Pd center and the carbonyl oxygen of the Boc group. However, when C2 is occupied by an aryl/alkyl substituent, 1,3-allylic strain[5] takes effect and results in an axial orientation (**ax-8** vs **eq-8**; entry 4). Without this interaction, diaxial repulsions dictate an equatorial orientation of the aryl/alkyl substituent (**eq-7** vs **ax-7**; entry 3).[4] In view of the energetic differences of the organometallic intermediates, the diastereoselectivity in the couplings of the piperidinylzinc reagents (**1** and **4**) may be determined at the stage of the respective Zn and Pd complexes. In the case of the couplings of the piperidin-2-ylzinc chlorides (**1**), there is strong evidence that the diastereoselectivity may already be introduced into the molecule via the

Scheme 2. 1,2-Migration of Pd in the Diastereoselective Cross-Coupling of *N*-Boc 6-Methylpiperidin-2-ylzinc Chloride



lithiation step.[3c,f,g,6] The thermodynamic preference for the Zn complexes with all substituents in equatorial positions may also contribute to the observed high diastereomeric ratios through dynamic thermodynamic resolution (DTR) processes.[15] For the piperidin-4-ylzinc iodides (**4**), the stereoselectivity is most likely introduced via a selective transmetalation step between the Zn reagent and the aryl−Pd complex, leading to the thermodynamically most stable intermediate, as proposed for the cyclohexyl systems,[4] although DTR processes on the Zn intermediates are also conceivable.

In continuation of our study, we found that arylations with the 6-methyl-substituted piperidin-2-ylzinc reagent **9** in the presence of $Pd(dba)_2$/RuPhos[8] as the catalyst system consistently resulted in the highly stereoselective formation of the 5-arylated, trans-configured products of type **11** (d.r. = 93:7 to 96:4),[16] whereas the expected trans-2,6-disubstituted products (**10**)[3c] were not obtained (Scheme 2). It is noteworthy that the coupling proceeded equally well with electron-rich (**11b**) and electron-poor (**11c**−**e**) aryl iodides. We assume that this reaction proceeds via β-hydride elimination of the Pd moiety.[17] The resulting $ArPdL_2H$[18] complex stays bound to the same side of the tetrahydropyridinyl ring, and its subsequent syn addition[19] places the Pd in the sterically less hindered position 5. Rapid reductive elimination furnishes the observed δ-arylated, 2,5-disubstituted coupling products (**11**). This Pd 1,2-migration/cross-coupling sequence seems to be a function of the nature and stoichiometry of the phosphine ligand. In our case, a Pd/RuPhos ratio of 1:1 was used. Coldham and Leonori[3c] reported the use of $Pd(OAc)_2$/*t*-Bu_3P with a ratio of 1:2 as the catalyst system, which may lead to a better stabilization of Pd(0) and thus prevent β-hydride elimination.

In conclusion, we have established a powerful methodology for the preparation of various substituted piperidines via highly diastereoselective Negishi cross-couplings[20] with (hetero)aryl iodides. Depending on the position of the C−Zn bond relative to the nitrogen (C2 vs C4), we were able to direct the stereoselectivity of the coupling toward either the trans- or cis-2,4-disubstituted products. A novel 1,2-migration of Pd expands our method to the synthesis of 5-arylated, 2,5-disubstituted piperidines. Investigations of the mechanism of this migration as well as further stereoselective arylations of saturated N-heterocycles are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental and computational details, NMR spectra, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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