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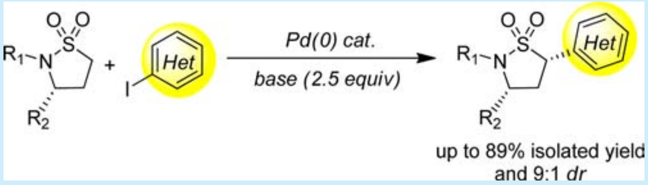
Palladium-Catalyzed α-Arylation of Sultams with Aryl and Heteroaryl Iodides

Olivier René,*,[†] Benjamin P. Fauber,[†] Sushant Malhotra,[‡] and Herbert Yajima[‡]

[†]Discovery Chemistry and [‡]Small Molecule Process Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, United States

Supporting Information

ABSTRACT: Palladium(0)-catalyzed conditions for the α-arylation of sultams with aryl and heteroaryl iodides have been developed. Arylation of 3-substituted 1,3-propanesultams gave rise to high yields and high diastereomeric ratios, leading to the thermodynamically favored *cis* product. The arylation was broadly applicable to various electron-rich and electron-poor (hetero)aromatic iodides.



In recent years, sultams (cyclic sulfonamides) have increasingly received significant attention due to their biological activity. Although not found in natural products,[1] several sultam-containing compounds have found medicinal uses in diverse therapeutic areas, such as oncology,[2] virology,[3] immunology,[4] treatment of neurological disorders,[5] and others.[6] As a result, a proliferating number of synthetic routes to access the sultam core have been reported.[7] Despite the large number of sultam ring-forming reactions, all of the reported methods require the desired functionalities around the carbon framework of the ring to be installed prior to the formation of the sultam ring.

As part of our research program, we became interested in establishing a method for late-stage incorporation of diverse arenes and heteroarenes onto a preformed sultam ring that would allow for rapid and divergent synthesis of C5-substituted analogues. We envisioned that the α-arylation of the sultam ring would be the most efficient transformation to accomplish this process, as it would not require any prefunctionalization of the C5 position of the sultam ring prior to the arylation step.

Although the α-arylation of carbonyl compounds is a well-established transformation,[8] the arylation of sulfonyl and sulfoxide compounds is a more challenging process due to the decreased acidity of the α-protons.[9] Reports include the Pd(0)-catalyzed arylation of methyl sulfoxides using a LiO*t*-Bu base.[9] There are also three-operation processes for the arylation of unactivated sulfones[10] and acyclic sulfonamides,[11] wherein deprotonation was first performed with a strong base, followed by transmetalation with $ZnCl_2$ prior to a Pd(0)-catalyzed Negishi-type cross-coupling. However, these methods were less applicable to the arylation of sultams, and as shown in Scheme 1, the reported three-operation process for the arylation of acyclic sulfonamides did not prove suitable for the arylation of their sultam counterpart.[12] Herein, we report an operationally simple one-step process for Pd(0)-catalyzed α-arylation of 1,3-propane sultams that features the use of TMPZnCl·LiCl[13] as the base. Furthermore, our process displays good diastereoselectivity for C3-substituted 1,3,-propanesultams bearing a sterically demanding substituent.

Initial reaction development and optimization on the Pd(0)-catalyzed α-arylation of sultam **1** using 10 mol % $Pd(dba)_2$, 10 mol % RuPhos, and iodobenzene in THF with various bases revealed the superiority of TMPZnCl·LiCl. The base could be used to activate the α-position *in situ*, obviating the need for a preactivation step. Other bases such as LiHMDS, KHMDS, NaO*t*-Bu, and TMPMgCl·LiCl[14] were not competent for the transformation and did not lead to formation of product. The use of iodobenzene also proved to be the optimal electrophile. With chlorobenzene (Table 1, entry 1) as the electrophile, the reaction reached 39% completion in 4 h, while bromobenzene (entry 2) gave 78% conversion. In the same amount of time, complete formation of product was observed with iodobenzene (entry 3).[15]

As shown in Table 1, the stoichiometry of the TMPZnCl·LiCl base was also essential in achieving both high conversion and diastereocontrol. For example, the use of only 1 equiv of base (entry 4) resulted in an incomplete conversion and a low diastereomeric ratio (dr) of 0.7:1 (*cis*:*trans*), only slightly favoring the *trans* diastereomer. Conversely, the use of a large excess (5 equiv) of base (entry 5) gave rise to a high dr of 10:1 (*cis*:*trans*), largely favoring the *cis* isomer, albeit in 77% conversion. The optimal amount of base was found to be 2.5 equiv (entry 3), which resulted in complete conversion to the *cis* sultam **2** in high dr. Additionally, subjecting a 1:12 mixture of **2**:**3** to TMPZnCl·LiCl (2.5 equiv) in THF at 60 °C afforded a 9:1 mixture of **2**:**3**. Presumably, sultam **2** was the thermodynamic product and the reaction selectivity was determined by the relative energy difference between the two diastereomers when an excess of base was used.

The use of other biaryl-type ligands did not provide notable changes in the reaction outcome, as illustrated with X-Phos

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Scheme 1. Previously Reported Three-Operation Arylation Process for Acyclic Sulfonamides Gave Low Yield with Sultam 1

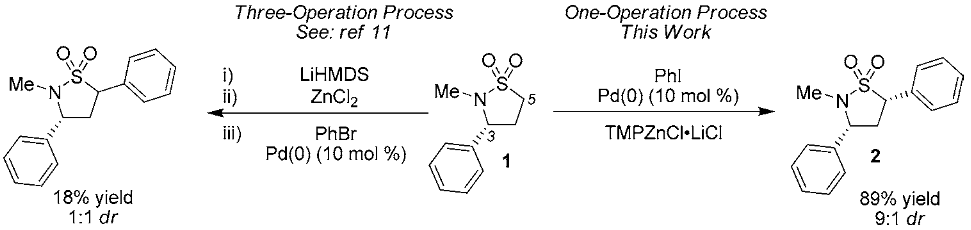
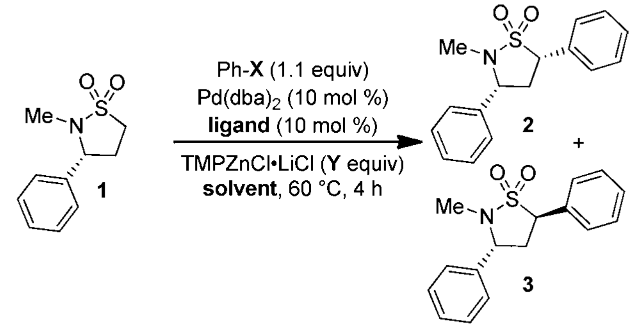
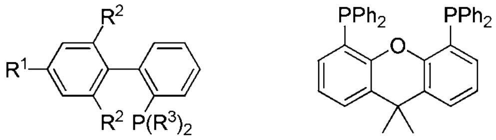


Table 1. Optimization of Reaction Conditions



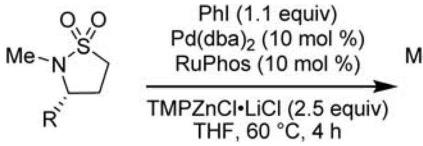


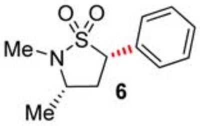
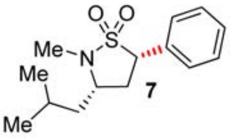
RuPhos: R^1 = H, R^2 = O*i*-Pr, R^3 = Cy
X-Phos: R^1 = R^2 = *i*-Pr, R^3 = Cy
JohnPhos: R^1 = R^2 = H, R^3 = *t*-Bu

entry	Ph-X	solvent	ligand	Y	convn (%)[a]	2:3[a]
1	Ph-Cl	THF	RuPhos	2.5	39	9:1
2	Ph-Br	THF	RuPhos	2.5	78	9:1
3	**Ph-I**	**THF**	**RuPhos**	**2.5**	**98**	**9:1**
4	Ph-I	THF	RuPhos	1.0	88	0.7:1
5	Ph-I	THF	RuPhos	5.0	77	10:1
6	Ph-I	THF	X-Phos	2.5	98	9:1
7	Ph-I	THF	JohnPhos	2.5	93	9:1
8	Ph-I	THF	Xantphos	2.5	46	10:1
9	Ph-I	THF	PPh_3	2.5	65	7:1
10	Ph-I	toluene	RuPhos	2.5	98	7:1

[a] Determined by HPLC analysis.

Table 2. Effect of the C3 Substituent on the Diastereoselectivity of the α-Arylation



entry	R	product	Isolated yield	dr[a]
1	Me **4**	 **6**	85%	2.5:1
2	*i*-Bu **5**	 **7**	75%	3:1
3	Ph **1**	 **2**	89%	9:1

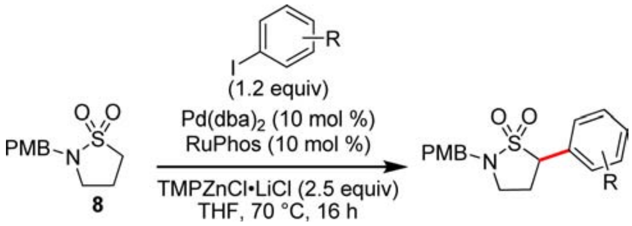
[a] Determined by unpurified ^{1}H NMR analysis of the sultam C5 proton

(Table 1, entry 6) and JohnPhos (entry 7). Bidentate ligand Xantphos (entry 8) and triphenylphosphine (entry 9) resulted in significantly lower conversions. The use of toluene as a solvent (entry 10) was also well tolerated with 98% conversion, albeit with a slightly lower dr.

Having established optimized conditions for the *α*-arylation of sultam **1**, we evaluated the applicability of the transformation with different C3 substituents on the sultam ring and the effect of the substituent size on the diastereomeric ratio. As illustrated in Table 2, the *α*-arylation reaction proceeded in high yield with R = methyl (Table 2, entry 1) with an isolated yield of 85% for product **6** and a 2.5:1 dr. The slightly more sterically demanding isobutyl-containing sultam (entry 2) also proved to be a suitable coupling partner and gave rise to the arylated product **7** in 75% yield, with a slightly improved 3:1 dr in favor of the *cis* product. Furthermore, the bulkier phenyl substituent (entry 3) gave the arylated product **2** in 89% isolated yield and 9:1 dr. Overall, it appears that the steric demand of the C3 substituent significantly contributes to the diastereomeric outcome of the reaction, with the bulkier substituent giving rise to the thermodynamically preferred *cis* product in high dr.[16]

Exploration of the scope of the aryl iodide coupling partner was accomplished using commercially available *N*-(4-methoxybenzyl)-1,3-propanesultam **8**, obviating the need for separating mixture of diastereomers and providing a suitable chromophore on the starting material for ease of purification. Illustrative examples of substituted arenes are shown in Table 3. Iodobenzene (Table 3, entry 1) performed similarly well in this system compared to the C3-substituted sultams and gave the desired product **9** in 82% yield. Additionally, electron-withdrawing substituents such as a *m*-cyano (entry 2) and *p*-methyl ester (entry 3) were suitable coupling partners and gave rise to the coupled products **10** and **11** in 41% and 52% yields, respectively. Interestingly, the chloro functionality (entry 4) was preserved under the reaction conditions, making it available for further functionalization, and provided arylated sultam **12** in 50% yield. Moreover, the electron-rich dioxine-bearing aryl iodide (entry 5) performed well and afforded product **13** in 87% yield. The more sterically hindered 1-iodonaphthalene (entry 6) and 1-iodo-2-methoxybenzene (entry 7) electrophiles gave rise to the corresponding arylated products **14** and **15** in 65% and 74% yields, respectively.

Table 3. Scope of Substituted Aryl Iodides



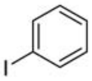
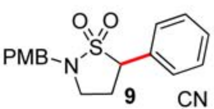
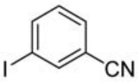
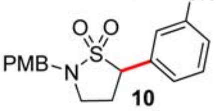
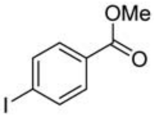
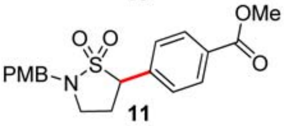
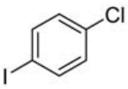
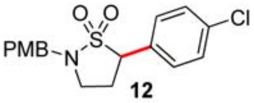
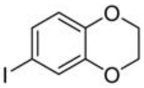
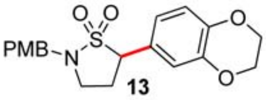
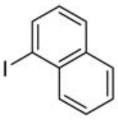
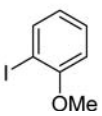
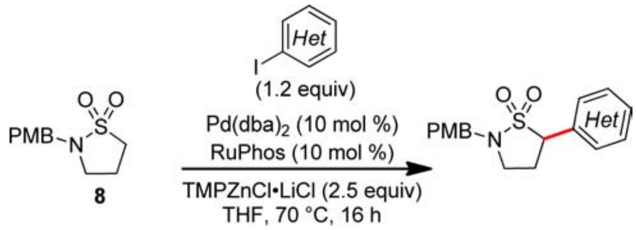
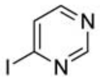
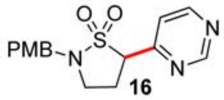
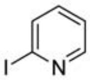
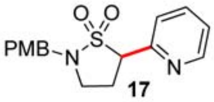
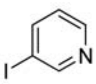
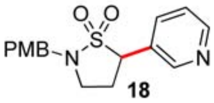
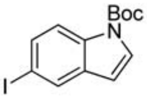
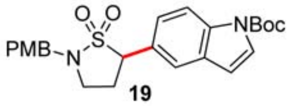
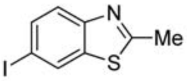
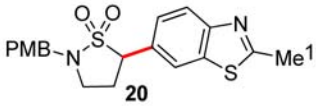
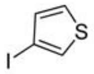
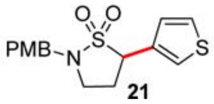
entry	aryl iodide	product	isolated yield
1		 **9**	82%
2		 **10**	41%
3		 **11**	52%
4		 **12**	50%
5		 **13**	87%
6		 **14**	65%
7		 **15**	74%

Table 4. Scope of Heteroaryl Iodides



entry	aryl iodide	product	isolated yield
1		 **16**	73%
2		 **17**	46%
3		 **18**	26%
4		 **19**	40%
5		 **20**	19%
6		 **21**	42%

We were also pleased to observe that the method was suitable for the α-arylation of our model sultam with a variety of heterocyclic iodides, as illustrated in Table 4. For example, 4-iodopyrimidine (Table 4, entry 1) coupled well and provided the desired product **16** in 73% yield. Other azine heterocycles such as 2-iodopyridine (entry 2) and 3-iodopyridine (entry 3) afforded the arylated sultams **17** and **18**, in yields of 46% and 26%, respectively. In addition, *N*-Boc-5-iodoindole, as well as 6-iodo-2-methylbenzo[*d*]thiazole, were competent coupling partners and provided the corresponding products **19** and **20** in moderate yield for the indole (entry 4) and low yield for the benzothiazole (entry 5). 3-Iodothiophene was also a suitable coupling partner and provided the arylated sultam **21** in 42% yield (entry 6).

Some observed limitations to the reaction included the use of certain heterocyclic iodides shown in Figure 1. Examples included azole-type heterocycles 3-iodo-1-methyl-1*H*-indazole and 4-iodo-1-methyl-1*H*-pyrazole, as well as 2-iodo-5-methylthiophene, which all gave <10% conversion by HPLC. Some azine-type heterocycles such as 2-iodopyrimidine or 4-chloro-6-iodoquinazoline, which contained a highly activated chloride, failed to provide the desired product in isolable quantities. Pd(0)-catalyzed cross-couplings with these types of heterocycles are typically considered to be challenging due to a difficult oxidative insertion of Pd(0) or to the ligation of the nitrogen-containing heterocycle onto palladium, which results in the displacement of the desired phosphine ligands, reducing the activity of the catalyst.[17] We also found that formation of a quaternary center by subjecting an α-substituted sultam to our reported conditions did not proceed. However, this matter is under further investigation.

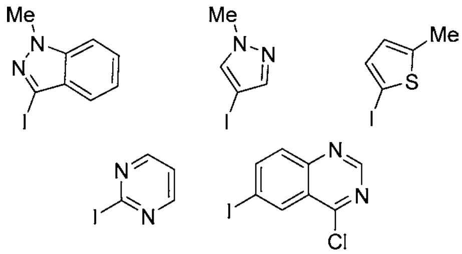


Figure 1. Unsuccessful heterocyclic iodides demonstrating the current limitations of the sultam α-arylation method.

In conclusion, we have developed general conditions for the α-arylation of sultams. The process was operationally simple and did not require preactivation of the sultam C−H bond prior to cross-coupling. A broad variety of substituted aryl iodides were compatible, such as electron-rich, electron-poor, and sterically hindered (hetero)aromatic iodides. In the presence of a C3 substituent on the sultam, moderate to high diastereomeric ratios were obtained, which were dictated by the steric hindrance of the substituent.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization with spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rene.olivier@gene.com.

Notes

The authors declare no competing financial interest.

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