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Cobalt-Catalyzed α-Arylation of Substituted α-Halogeno β-Lactams

Vanessa Koch,[‡,†,∥] Mélanie M. Lorion,[†,∥] Etienne Barde,[†] Stefan Bräse,[‡,§] and Janine Cossy*[,†]

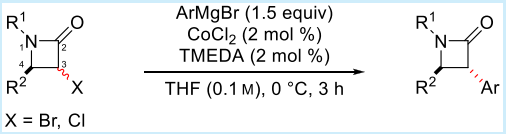
[†]Molecular, Macromolecular Chemistry and Materials (C3M), ESPCI Paris, CNRS, PSL University, 10 rue Vauquelin, 75231 Paris Cedex 05, France

[‡]Institute for Organic Chemistry (IOC), Karlsruhe Institute for Technology (KIT), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany

[§]Institute for Toxicology and Genetics (ITG), Hermann-von-Helmholtz Platz 1, 76344 Eggenstein-Leopoldshafen, Germany

Supporting Information

ABSTRACT: The treatment of 3-bromo β-lactams by an aryl Grignard, in the presence of $CoCl_2$ (2 mol %) and TMEDA (2 mol %) in THF, produces 3-aryl β-lactams in good yields and excellent diastereoselectivity.



More than 90 years after Fleming's discovery of the antibiotic effects of the fungal metabolite penicillin,[1] β-lactam antibiotics are still one of the most powerful medicines to treat infections. However, the first synthesis of a β-lactam was reported in 1907 by Staudinger,[2] and several years of intense research were required to determine the structure of penicillin[3] and to connect the core structure with a Staudinger β-lactam (Figure 1). Since then, β-lactams and azetidin-2-ones have been intensively studied, their relevance as antibiotics increased, and other β-lactam antibiotics such as cephalosporins, carbapenems, and monobactams appeared on the market.[4,5] In addition, β-lactams are considered interesting building blocks[6] for the synthesis of nitrogen-containing compounds of biological relevance which resulted in Ojima's introduction of the so-called "β-lactam synthon method" strategy.[7] Because of the ring strain, β-lactams can be easily opened by nucleophiles and are therefore well-known precursors of β-amino alcohols and β-amino acids. In addition, their rearrangements can lead to *N*-containing heterocyclic compounds of medicinal interest such as pyrrolidines, pyridones, and oxazinones.[6,8]

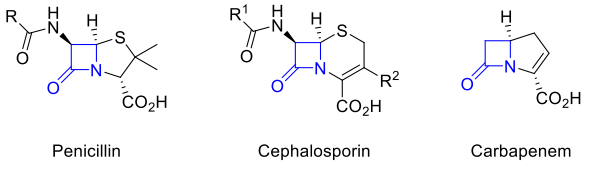
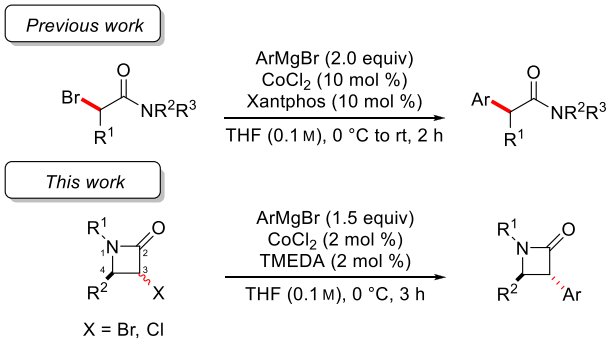


Figure 1. β-Lactam antibiotics.

The functionalization of heterocycles by cross-coupling has proved to be powerful tools to access a library of compounds from a lead in order to find a molecule with better biological activity than the lead itself. While tremendous advances have been achieved through the use of the well-established palladium-catalyzed cross-couplings[9] in the past 50 years, focus has been shifted toward the use of earth-abundant and inexpensive 3d-metal catalysts.[10−13] Besides the low costs of the catalytic system, these metal catalysts are less prone to induce dehalogenation or β-elimination than palladium catalysts, allowing the functionalization of alkyl halides.

Following up on our previous work on cobalt-catalyzed cross-couplings between α-bromo amides and Grignard reagents,[10b,14] we would like to report herein a cobalt-catalyzed α-arylation of 3-halogeno β-lactams by utilizing inexpensive and commercially available or easily accessible Grignard reagents to access potential pharmaceutically interesting 3-aryl azetidin-2-ones (Scheme 1).

Scheme 1. Co-Catalyzed α-Arylation of Amides and Lactams by Grignard Reagents



A Staudinger [2+2]-cycloaddition of aryl imines with α-halo acetyl halides under basic conditions was selected for the synthesis of the *trans*-3-halo 4-aryl-β-lactams **1**.[15] Based on our previous results on the Co-catalyzed cross-coupling of α-bromo amides, we started our investigations on the *trans*-3-bromo 4-aryl-β-lactam **1a**, using an equimolar mixture of $CoCl_2$ (10 mol %) and XantPhos (10 mol %) as the catalytic system. The Grignard reagent, the *p*-tolylmagnesium bromide (*p*-TolMgBr) (1.50 equiv) in THF (c = 0.76 M) was added dropwise to the reaction mixture at 0 °C. After 3 h, the desired *trans*-3-aryl

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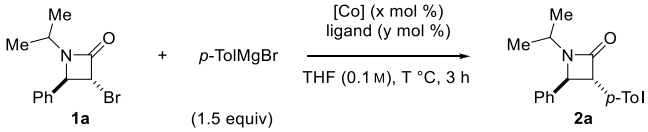
β-lactam **2a** was isolated in 34% yield (Table 1, entry 1). While the use of both mono- and bidentate phosphine ligands such as PPh_3, dppf, or dppe did not lead to any improvement in the yield of **2a** (see Table S1, Supporting Information (SI)), nitrogen-based ligands such as tetramethyl ethylenediamine (TMEDA) and *trans*-tetramethyl cyclohexan-1,2-diamine (TMCD) proved to be determining for the yield in the cross-coupling product, as **2a** was isolated in 68% when TMEDA was used and in 66% yield when TMCD was utilized (Table 1, entries 2−3).

To our delight, the inexpensive $CoCl_2$ proved to be superior to other cobalt sources such as CoF_2, $CoBr_2$, CoI_2, $Co(acac)_2$, and $Co(OAc)_2$ (Table 1, entries 5−9). The importance of the cobalt catalyst and ligand was demonstrated by control experiments, as without the catalyst or ligand, no conversion or poor conversion of **1a** was obtained (Table 1, entries 4 and 11). It is worth mentioning that if a turbo Grignard reagent (Mg/LiCl then addition of Dibal-H followed by the addition of *p*-TolBr) was used instead of the commercially available Grignard reagent, only 32% of **2a** was isolated (versus 68%) which goes along with the poor yield obtained when LiCl was introduced in the reaction media as an additive (see SI). When the reaction was conducted at −20 °C instead of 0 °C, the yield of **2a** was increased to 67% (Table 1, entry 10). Further improvements were achieved by adding the Grignard reagent with a syringe pump (2.4 mL/h for 1.5 mL of *p*-TolMgBr solution in THF, c = 0.76 M) resulting in a 76% yield of **2a** on a 0.75 mmol scale (Table 1, entry 12). Noteworthy, the amount of $CoCl_2$ and TMEDA could be lowered to 2 mol % without any decrease of the yield in **2a** (Table 1, entries 13−14). Moreover, the reaction could be performed on a 2.0 mmol scale without affecting the yield of the coupling product (Table 1, entry 15). It worth mentioning that when 3-chloro β-lactam **1a′** instead of 3-bromo β-lactam **1a** was involved in the coupling, the desired 3-aryl β-lactam **2a** was isolated with a lower yield of 52%, nevertheless still satisfactory (Table 1, entry 16).

With the optimized conditions in hand, the substrate scope was explored, starting with a range of 3-bromo β-lactams **1a−q**, substituted at C4 by different aryl groups (Scheme 2).

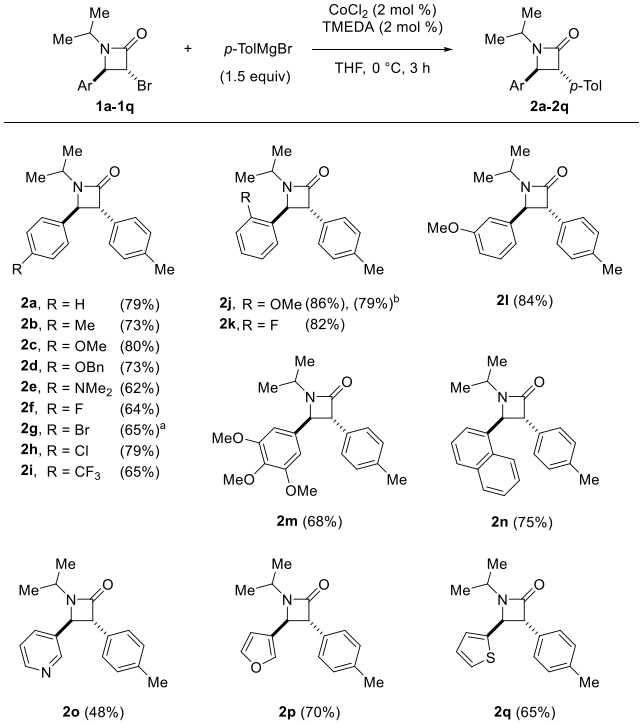
Table 1. Optimization of the Cross-Coupling Conditions[a]



entry	[Co] (x mol %)	ligand (y mol %)	T (°C)	yield
1	$CoCl_2$ (10)	XantPhos (10)	0	34%
2	$CoCl_2$ (10)	TMEDA (10)	0	68%
3	$CoCl_2$ (10)	TMCD (10)	0	66%
4	–	TMEDA (10)	0	0%
5	CoF_2 (10)	TMEDA (10)	0	0%
6	$CoBr_2$ (10)	TMEDA (10)	0	47%
7	CoI_2 (10)	TMEDA (10)	0	45%
8	$Co(acac)_2$ (10)	TMEDA (10)	0	41%
9	$Co(OAc)_2$ (10)	TMEDA (10)	0	31%
10[b]	$CoCl_2$ (10)	TMEDA (10)	−20	67%
11	$CoCl_2$ (10)	–	0	20%
12[c]	$CoCl_2$ (10)	TMEDA (10)	0	76%
13[c]	$CoCl_2$ (5)	TMEDA (5)	0	82%
14[c]	**$CoCl_2$ (2)**	**TMEDA (2)**	**0**	**79%**
15[d]	$CoCl_2$ (2)	TMEDA (2)	0	73%
16[c,e]	$CoCl_2$ (2)	TMEDA (2)	0	52%

[a]Reaction conditions: **1a** (0.225 mmol), *p*-TolMgBr (2.00 equiv), 3 h; yields of isolated products. [b]At 25 °C, the yield is similar (69%) but leads to a tedious purification due to the presence of dehalogenated byproducts. [c]**1a** (0.750 mmol), *p*-TolMgBr (1.50 equiv). [d]**1a** (2.00 mmol), *p*-TolMgBr (1.50 equiv). [e]Using 3,4-*trans*-3-chloro 1-isopropyl-4-phenylazetidin-2-one **1a′**.

Scheme 2. Variation of the α-Bromo β-Lactams 1



[a]Obtained as a mixture of **2g**, double-coupling product and dehalogenated product in a ratio of 1:0.16:0.06 according to ^{1}H NMR spectra analysis (see SI). [b]Using 3,4-*cis*-**1j**.

Regardless of the electronic character of the substituent at the *para*-position of the aryl group present at C4, e.g. an electron-donating or an electron-withdrawing substituent, the corresponding cross-coupling products were obtained with good yields ranging from 64% to 79%. Even the presence of a *p*-bromo- (**1g**) or a *p*-chloro- (**1h**) substituent on the aromatic was well-tolerated allowing further derivatization. In the case of a *p*-bromo substituent (**1g**), the coupling product **2g** was isolated along with a small amount of the double coupled product and the debrominated product (see SI), showing that the cross-coupling of the *p*-TolMgBr with the halide on the β-lactam ring was strongly favored over the coupling with the aryl halide. Gratifyingly, the reaction was not sensitive to steric hindrance, as the 3-bromo β-lactams, substituted at C4 by a *p*-, *o*-, or *m*-methoxy-phenyl group, were efficiently coupled with *p*-TolMgBr, delivering the expected β-lactams **2c**, **2j**, and **2l** with very good yields (around 80%). Interestingly, when the 3,4-*cis*-**1j** and 3,4-*trans*-**1j** were separately subjected to the cross-coupling conditions, both compounds exclusively led to the 3,4-*trans* β-lactam **2j** (see SI). The assignment of the relative configuration of the substituents was achieved by measurements of the ^{1}H NMR coupling constants between the protons at C3 and C4 of the obtained products ($^3J \sim 2.2$ Hz) which correspond to those reported for *trans*-β-lactams.[16] Moreover, polysubstituted aromatics can be present at the C4 position of the

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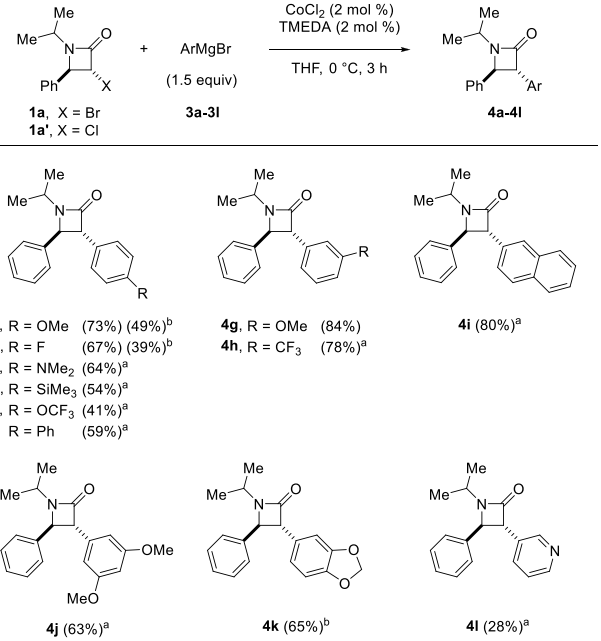
β-lactam without any decrease of the yield as **2m** was isolated in 68% yield when a 3,4,5-trimethoxy substituted aryl group is present. When the β-lactam is substituted by a 1-naphthyl substituent (**1n**), the coupling product **3n** was successfully formed in 75% yield. Heterocycles are also well-tolerated as shown for β-lactams substituted at C4 by a 3-pyridyl, 3-furyl, and 2-thiophenyl, as 3-aryl β-lactams **2o**, **2p**, and **2q** were isolated in 48%, 70%, and 65% yields, respectively.

To diversify the β-lactam substituents at C3, various aryl Grignard reagents were involved in the cross-coupling with 3-bromo 4-phenyl β-lactam **1a** (Scheme 3). Both electron-rich *p*-methoxyphenylmagnesium bromide and electron-poor *p*-fluorophenylmagnesium bromide were efficiently coupled to the 3-bromo β-lactam **1a**, delivering the corresponding coupling products **4a** and **4b** in good yields (= 70%). When the 3-chloro β-lactam **1a′** was used, the cross-coupling was less efficient than with the 3-bromo β-lactam **1a**, resulting in the formation of **4a** and **4b** in lower yields of 49% and 39%, respectively, along with nonidentified side products. We could also demonstrate that several functional groups such as a *N*,*N*-dimethyl-amino-, trimethylsilyl-, and trifluoromethoxy group on the aryl Grignard reagents **3** were tolerated, as the coupling products **4c**−**4e** were isolated in satisfying yields (41−64%). The aromatic system of the aryl Grignard can also be successfully extended to biphenyl-4-yl (**1f**) and 2-naphthyl (**1i**) systems. While *ortho*-functionalization of the aryl Grignard reagents did not lead to full conversion of **1a**, a *meta*-substitution was well-tolerated and gave the corresponding products in good yields as shown when *m*-methoxyphenyl-magnesium bromide (**4g**: 63%), 3,5-dimethoxyphenyl-magnesium bromide (**4j**: 63%), and *m*-(trifluoromethyl)phenylmagnesium bromide were used. To our delight, also a benzo[1,3]dioxole moiety could be introduced with 65% yield (**4k**). Although with a lower yield, a pyridyl substituent can be introduced at the C3 position of the β-lactam (**4l**).

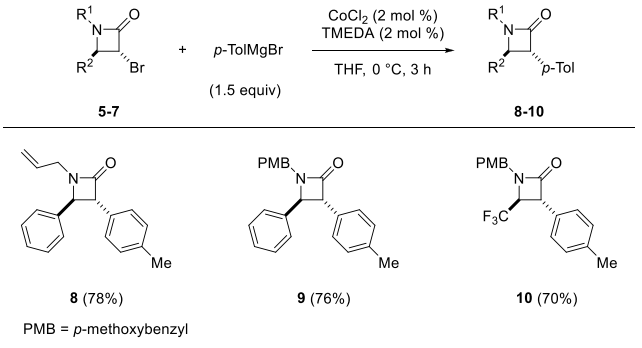
Scheme 3. Variation of the Grignard Reagents 3



[a]The Grignard reagent was prepared using Mg turnings in THF. [b]Using 3,4-*trans*-3-chloro 1-isopropyl-4-phenylazetidin-2-one **1a′**.

Moreover, the nitrogen protecting group of the β-lactam has no impact on the yield of the cobalt-catalyzed cross-coupling between 3-bromo β-lactams and aryl Grignard reagents (Scheme 4). Thus, when the *N*-isopropyl group was replaced by removable protecting groups such as an *N*-allyl- or an *N*-*p*-methoxybenzyl- (PMB) group, and by using *p*-tolylmagnesium bromide as the Grignard reagent, the cross-coupling products **8** and **9** were obtained in good yields (76%−78%). Furthermore, when a trifluoromethyl group is present at C3 on the β-lactam instead of an aryl group, the outcome of the cross-coupling was not influenced. In this case, the thermodynamically favored cross-coupling product was the *trans*-3-tolyl 4-trifluoromethyl-β-lactam **10** which was exclusively formed from the corresponding *cis*-3-bromo 4-trifluoromethyl-β-lactam.

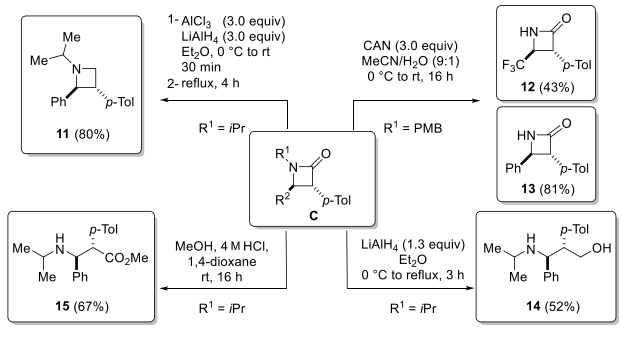
Scheme 4. Variation of the *N*-Protecting Groups and C4 Substituents



To show the synthetic utility of the prepared α-aryl β-lactams, synthetic transformations of these latter were realized (Scheme 5). For example, treatment of **2a** with AlH_3 provided azitidine **11** in 80% yield showing that the carbonyl group of the azetidin-3-one can be easily removed. We also demonstrated that the *N*-PMB group can be cleaved to afford the free β-lactams **12** and **13**. Furthermore, the α-aryl β-lactam **1a** was reductively opened with $LiAlH_4$ to give access to the corresponding γ-amino alcohol **14** and the acidic methanolysis of the α-aryl β-lactam delivered the *N*-protected β-amino ester **15** in good yield (67%).

In summary, a highly efficient and inexpensive cobalt-catalyzed α-arylation of pharmaceutically and biologically relevant β-lactams was developed with only 2 mol % of $CoCl_2$ and TMEDA. An array of functional groups is tolerated by the herein reported reaction conditions, and different Grignard reagents can be involved in the cross-coupling providing a diversity of α-aryl β-lactams in good yields.

Scheme 5. Diversification of the α-Arylated β-Lactams



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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02122.

Experimental procedures, characterization data, and ^{1}H, ^{13}C, and ^{19}F NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: janine.cossy@espci.fr.

ORCID

Mélanie M. Lorion: 0000-0002-5816-9103

Janine Cossy: 0000-0001-8746-9239

Author Contributions

‖V.K. and M.M.L. contributed equally.

Notes

The authors declare no competing financial interest.

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