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# Cobalt-Catalyzed $\alpha$ -Arylation of Substituted $\alpha$ -Bromo $\alpha$ -Fluoro $\beta$ -Lactams with Diaryl Zinc Reagents. Generalization to Functionalized Bromo Derivatives.

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## Abstract:

A Cobalt-catalyzed cross-coupling of  $\alpha$ -bromo  $\alpha$ -fluoro  $\beta$ -lactams with diarylzinc or diallylzinc reagents is herein disclosed. The protocol proved to be general, chemoselective and operationally simple allowing the C4 functionalization of  $\beta$ -lactams. The substrate scope was expanded to  $\alpha$ -bromo lactams and amides,  $\alpha$ -bromo lactones and esters as well as *N*- and *O*-containing heterocycles.

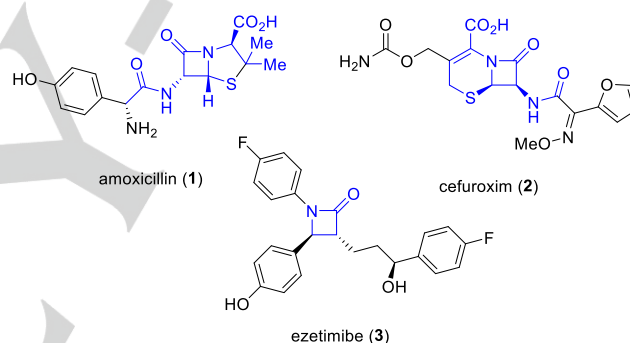


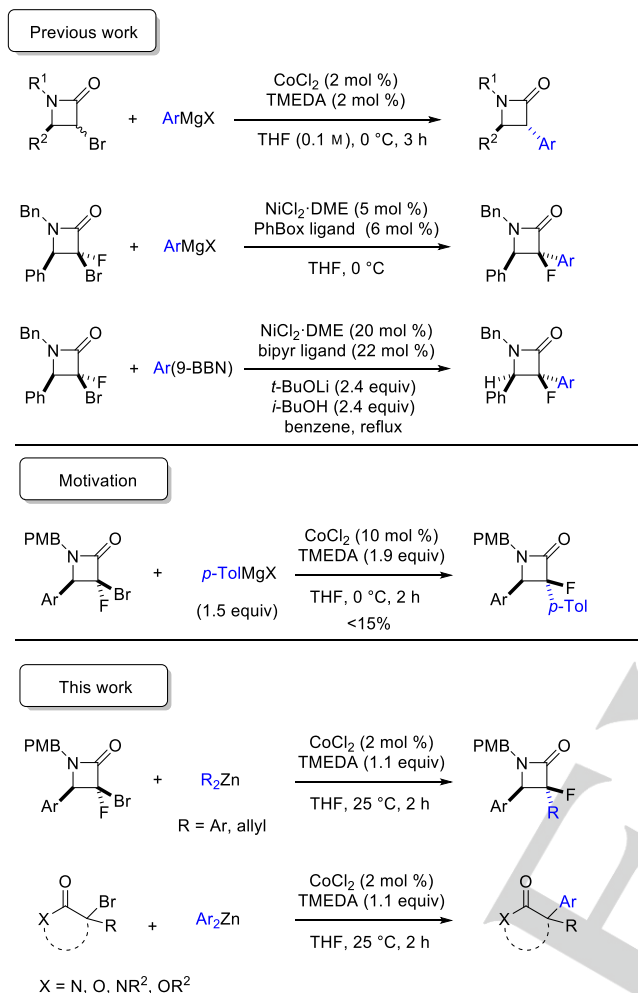
Figure 1. Medically important bioactive  $\beta$ -lactams (1–3).

## Introduction

The incorporation of fluorine into bioactive compounds to improve their pharmacological properties has been well-established in the drug research resulting in more than 100 fluorine-containing compounds being approved by the FDA (Food and Drug Administration) in the US. Notably, the vast majority of the top-selling drugs worldwide include at least one fluorine atom.<sup>[1]</sup> The remarkable changes in biological and pharmacological properties induced by the replacement of a hydrogen atom by a fluorine atom can be explained by its unique properties such as its lipophilicity, high electronegativity and oxidation potential (−3.06 V), the high C–F bond strength and the capacity of a fluorine atom to be involved in polar interactions and hydrogen bonding while maintaining the size of the molecule (the radius of a fluorine is only 12.5% larger than that of hydrogen).<sup>[2]</sup> These properties are influencing important parameters of a drug such as its solubility, stability, bioavailability and its binding to proteins which can therefore lead to significant effects on its absorption, distribution and clearance.<sup>[1–2, 3]</sup>

$\beta$ -Lactams are a class of bioactive compounds with antibacterial properties<sup>[4]</sup> (Figure 1) as well as useful chiral building blocks in organic synthesis as they can be transformed to  $\beta$ -amino acids by ring-opening.<sup>[5]</sup> Besides to  $\beta$ -lactams with antibacterial activity such as penicillin (e.g. amoxicillin **1**) and cephalosporin (e.g. cefuroxime **2**), they can also inhibit different types of enzymes.<sup>[6]</sup> For example, ezetimibe **3** is used to treat high blood cholesterol by inhibiting the cholesterol transporter NPC1L,<sup>[7]</sup> showing that modifications at the C3 and C4 positions of the  $\beta$ -lactam ring has an impact on the biological activity of  $\beta$ -lactams. Thus, it is important to develop efficient methods allowing the introduction of different substituents and/or fluorine atoms at the C4 position of a  $\beta$ -lactam to modify and/or increase the bioactivity of these lactams. The incorporation of fluorine atoms onto a  $\beta$ -lactam ring has been mainly pioneered by Tarui *et al.* who explored the synthesis of several racemic and optically active fluorinated  $\beta$ -lactams.<sup>[8]</sup> In addition, a diversity of substituted  $\beta$ -lactams were synthesized either by Ni-catalyzed cross-coupling (Scheme 1),<sup>[9]</sup> or by direct alkylation or aldolization.<sup>[10]</sup> Herein, we report the  $\alpha$ -arylation of  $\alpha$ -bromo  $\alpha$ -fluoro  $\beta$ -lactams which could not be conducted using Grignard reagents under cobalt-catalyzed cross-coupling, using the conditions developed in one of our group,<sup>[11a]</sup> but could be achieved by using diarylzinc

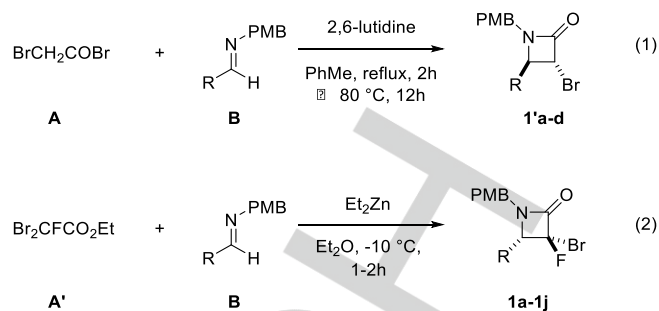
and diallylzinc reagents (Scheme 1). The reaction is general and can be applied to a range of  $\alpha$ -bromo carbonyl derivatives such as  $\alpha$ -bromo  $\beta$ -lactams and amides as well as  $\alpha$ -bromo lactones and esters.



**Scheme 1.**  $\alpha$ -Arylation and  $\alpha$ -alkylation of lactams and lactones.

## Results and Discussion

Different methods have been developed to access  $\beta$ -lactams including the cyclization of  $\beta$ -amino-acids or Staudinger reactions and transition-metal catalyzed reactions, photocatalysis or C–H activation/amidation.<sup>[12]</sup> Among these methods, we chose the Staudinger (2+2)-cycloaddition between  $\alpha$ -bromo acetyl halide (**A**) and the aryl imines **B** which allow the access to  $\alpha$ -bromo  $\beta$ -lactams **1** (Scheme 2). A Reformatsky-type reaction,<sup>[8b, 8c]</sup> involving ethyl dibromofluoroacetate (**A'**) and imines **B**, in the presence of an excess of Et<sub>2</sub>Zn was utilized to synthesize  $\alpha$ -bromo  $\alpha$ -fluoro  $\beta$ -lactams (**1a–1j**). The relative configuration was reported to be *cis* (related to the position of F/H) with a coupling constant of <sup>3</sup>J ~ 10.3 Hz between the fluorine atom at C3 and the proton at C4<sup>[8b, 9]</sup> and the structure of **1h** was confirmed by X-ray diffraction of **1h** (see SI).

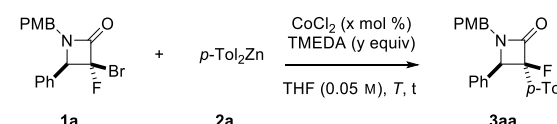


**Scheme 2.** Synthesis of  $\alpha$ -bromo- $\beta$ -lactam **1** and  $\alpha$ -bromo  $\alpha$ -fluoro- $\beta$ -lactams, **1a–1j**.

Based on our previous results on cobalt-catalyzed cross-coupling of  $\alpha$ -bromo  $\beta$ -lactams with aryl Grignard reagents, we started our investigations on the *trans*-3-bromo 3-fluoro 4-aryl  $\beta$ -lactam **1a** using CoCl<sub>2</sub> (10 mol %), tetramethylethylenediamine (TMEDA, 1.9 equiv) and the Grignard reagent *p*-TolMgBr **2a** (1.5 equiv), in THF at 0 °C. Under these conditions, only traces of the desired product **3aa** were observed (less than 15%).<sup>[11b]</sup> Due to this failure, organo-zinc reagents, which show a greater functional group tolerance and are therefore widely utilized in cross-couplings,<sup>[13]</sup> were envisaged. While the use of the heteroleptic arylzinc reagent, *p*-TolZnCl, was not effective, the use of freshly prepared bis(*p*-tolyl)zinc (Tol<sub>2</sub>Zn) led to the formation of the desired cross-coupling product **3aa**. The relative configurations of the cross-coupled product were determined by measurement of the <sup>1</sup>H NMR coupling constant between the fluorine atom at C3 and the proton at C4 (<sup>3</sup>J ~ 3.5 Hz) which corresponds to the coupling constant reported for  $\alpha$ -fluoro  $\beta$ -lactams with a *trans* configuration (related to the position of F/H).<sup>[8b, 9]</sup> The cross-coupling was performed by adding a solution of *p*-Tol<sub>2</sub>Zn in THF (2.0 equiv, *c* was determined each time by titration) over 15 min using a syringe pump, to a solution of **1a** (0.25 mmol) containing CoCl<sub>2</sub> (10 mol %) and TMEDA (1.9 equiv) at 0 °C. After stirring for 3 h at 0 °C and after raising up the temperature to rt, the desired 3-fluoro 3-*p*-tolyl  $\beta$ -lactam **3aa** was formed in 75% yield which was calculated by <sup>1</sup>H NMR analysis (Table 1, entry 1). While lowering the amount of Tol<sub>2</sub>Zn to 1.5 equiv did not impact the outcome of the reaction, the use of only 0.6 equiv did not result in full conversion of the starting material **1a** and, as consequence, a modest yield of 55% in **3aa** was obtained (evaluated by <sup>1</sup>H NMR) (Table 1, entries 2–3). To our delight, the reaction could be run at rt without any remarkable influence on the reaction outcome (Table 1, entry 4) and, in addition, the reaction time could be reduced to 2 h affording **3aa** in 79% isolated yield (Table 1, entry 5). The influence of TMEDA was also studied revealing that a catalytic amount of TMEDA (20 mol %) was not sufficient as the yield in **3aa** dropped to 50% (Table 1, entry 7). It is worth mentioning, that an enhancement of the yield of the products resulting of the cross-coupling between  $\alpha$ -bromo  $\alpha$ -fluoro compounds and arylzinc reagents was already observed by Araki *et al.* when an arylzinc-TMEDA complex was utilized.<sup>[14]</sup> These results suggest that TMEDA can act both as a ligand and an additive. Nevertheless, the amount of TMEDA could be successfully reduced to 1.1 equiv (Table 1, entry 6). Noteworthy, the amount of CoCl<sub>2</sub> could also be reduced

to 2.0 mol % without any decrease of the yield in **3aa** (Table 1, entry 8). Control experiments showed the importance of the cobalt catalyst and of the ligand as, without them, the formation of the desired product was not observed (Table 1, entries 9 and 10).

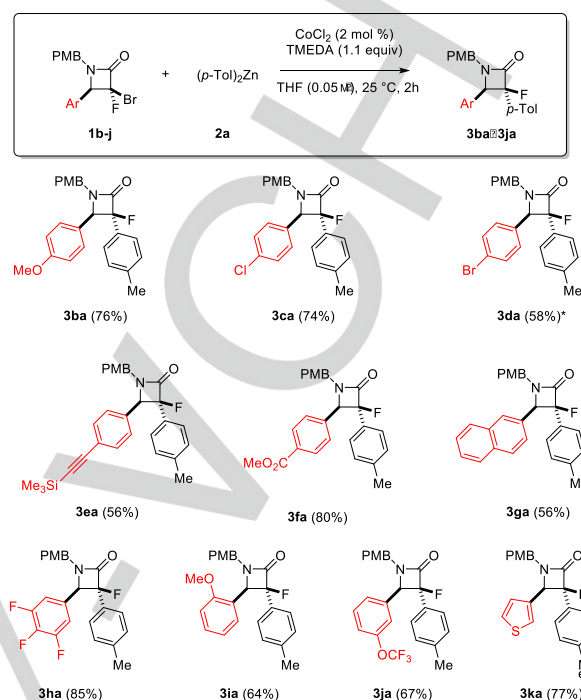
**Table 1.** Optimization of the cross-coupling conditions<sup>a</sup>.

						
Entry	CoCl <sub>2</sub> (x mol %)	TMEDA (y equiv)	Tol <sub>2</sub> Zn (z equiv)	T [°C]	t (h)	Yield [%]
1	10	1.9	2.0	0	16	75
2	10	1.9	1.5	0	16	71
3	10	1.9	0.6	0	16	55
4	10	1.9	1.5	25	16	79
5	10	1.9	1.5	25	2	79
6	10	1.1	1.5	25	16	80 [72]
7	10	0.2	1.5	25	16	50 [51]
8	2	1.1	1.05	25	2	78 [75]
9	-	1.1	1.05	25	2	-
10	-	-	1.05	25	2	-

[a] Reaction conditions: **1a** (0.25 mmol); yields are based on <sup>1</sup>H NMR analysis of the crude reaction using 1,3,5-trimethoxybenzene as internal standard; yields for the isolated products **2a** are given in brackets.

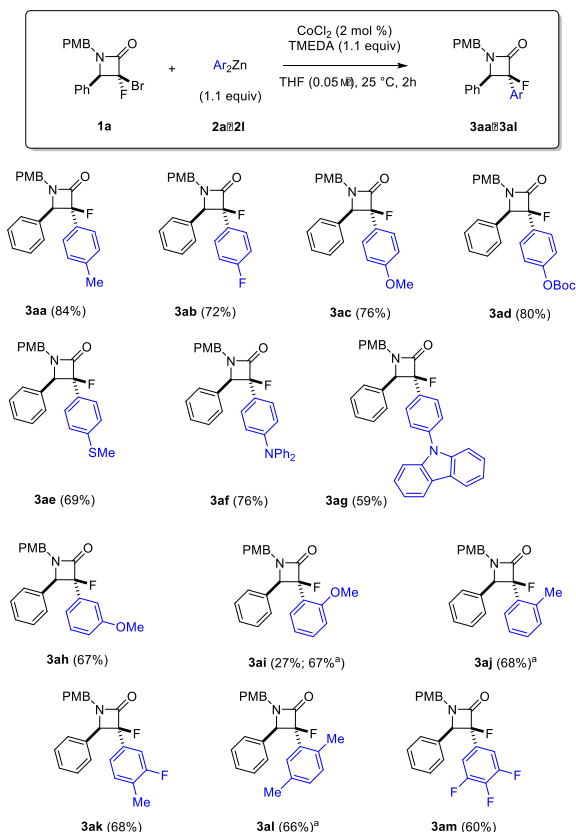
With the optimized conditions in hand, the substrate scope was explored, starting with a range of different C4-substituted  $\alpha$ -bromo  $\alpha$ -fluoro  $\beta$ -lactams (**1b–1j**) (Scheme 3). No dependency on the electronic character of the substituent at the *para*-position of the aryl group present at C4 was observed as the corresponding cross-coupling products (**3ba–3fa**) were obtained with yields ranging from 56% to 80%. A *p*-chloro- (**3ca**, 74%) and *p*-bromo (**3da**, 58%) as well as the *p*-TMS-ethynyl (**3ea**, 56%) substituents were well-tolerated and could further be involved in cross-couplings. In the case of a *p*-bromophenyl substituent, the coupling product (**3da**) was isolated along with the debrominated cross-coupled product (12%) (see SI). Due to the higher functional group tolerance of the (*p*-Tol)<sub>2</sub>Zn reagent compared to the (*p*-Tol)MgBr, an ester group remained untouched, giving the cross-coupled product **3fa** in good yield (80%). A 2-naphthyl substituent or a strong electron-withdrawing 3,4,5-trifluorophenyl substituent at C4 delivered the corresponding products in **3ga** in 56% and **3ha** in 85% yield, respectively. Furthermore, the reaction is not sensitive to steric hindrance, since both an *o*-methoxy and a *m*-trifluoromethoxy substituent did not influence the reaction outcome as the coupling products were isolated in 64% (**3ia**) and 67% yield (**3ja**).

The presence of a 2-thiophenyl moiety at C4 as a prominent representative of heterocycles, was not detrimental to the coupling reaction as **3ka** was isolated in 77% yield.



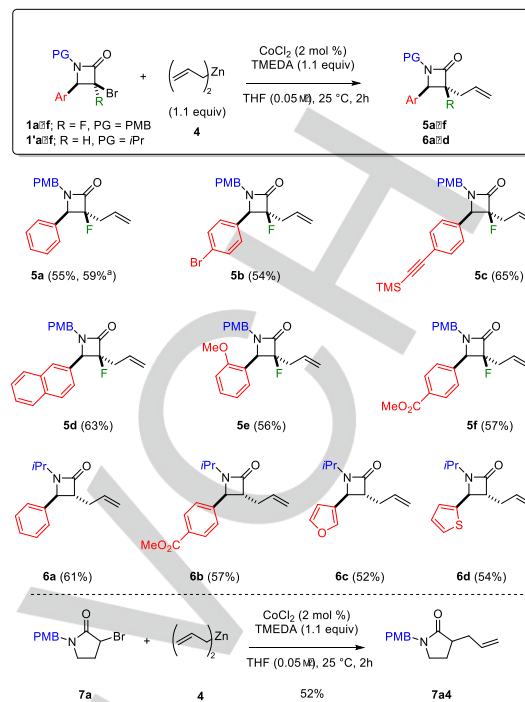
**Scheme 3.** Cobalt-catalyzed cross-coupling of C4-substituted  $\alpha$ -bromo  $\alpha$ -fluoro  $\beta$ -lactams (**1b–1j**) with bis(*p*-tolyl)zinc **2a**. \* **3da** product was isolated as a mixture with the dehalogenated cross-coupled product (12%).

In order to introduce a diversity of substituents at C3 on the  $\alpha$ -fluoro  $\beta$ -lactam ring, different diarylzinc reagents were synthesized and involved in the cross-coupling. The expected cross-coupling products **3aa–3al** were isolated with overall good yields, ranging from 59% to 80% (Scheme 4). Both electron-rich as well as electron-poor diarylzinc reagents were successfully coupled to the  $\alpha$ -bromo  $\alpha$ -fluoro  $\beta$ -lactam **1a** regardless of the electronic nature of the aryl group of the diarylzinc reagent. We were also able to show that several functional groups can be tolerated on the aryl group of the diarylzinc reagents such as a OBoc (**2d**), a SMe (**2e**), and an amino substituent (**2f**), as well as a carbazole (**2g**). The corresponding coupling products **3ad–3ag** were isolated in good yields (59–80%). While the *meta*-functionalization did not cause any problems as shown with the presence of a *m*-methoxy group on the diarylzinc reagent (**3ah**: 67%), a significant drop in yield was observed when an *ortho* substituent is present on the aryl group as the use of the bis(*o*-methoxyphenyl)zinc reagent led to **3ai** in only 27% yield.<sup>[15]</sup> In order to improve the yield of **3ai**, 10 mol % CoCl<sub>2</sub> were used and, under these conditions, **3ai** was isolated in 67% yield. Similar results were obtained when using the bis(*o*-tolyl)zinc **2j** reagent giving the corresponding product **2aj** in 68% yield. Moreover, double functionalized diarylzinc reagents were efficiently cross-coupled with **1a** delivering **3ak** and **3al** in 68% and 66%, respectively.



**Scheme 4.** Cobalt-catalyzed cross-coupling of  $\alpha$ -bromo  $\alpha$ -fluoro  $\beta$ -lactam **1a** with diarylzinc reagents **2a–2m**. [a] 10 mol % of  $\text{CoCl}_2$  was used.

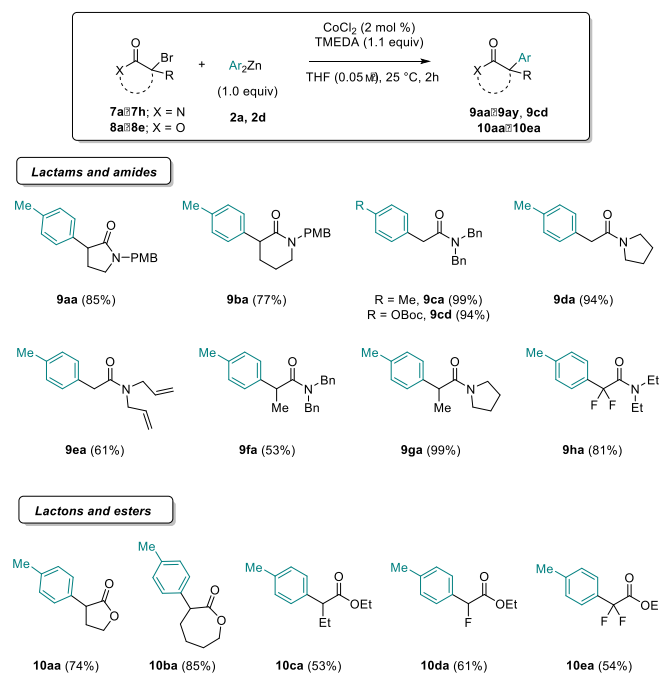
In contrast to the cobalt-catalyzed cross-coupling with Grignard reagents, we were able to efficiently introduce an allyl group at the C3 position of  $\beta$ -lactams as the use of diallylzinc (**4**) delivered the corresponding cross-coupled products **5a–5f** and **6a–6c** in yields ranging from 48% to 65% yield (Scheme 5).<sup>[16]</sup> Regardless of the amount of  $\text{CoCl}_2$  (2 or 10 mol %), the cross-coupled  $\alpha$ -fluoro  $\beta$ -lactam **5a** was obtained in comparable yields of 55% and 59%. For comparison, when the non-fluorinated  $\beta$ -lactam was treated with diallylzinc under the same conditions, the cross-coupled product **6a** was isolated in a comparable yield of 61%. Interestingly, neither the electronic character of the aryl at C4 nor the steric hindrance, showed an effect on the cross-coupling as shown for the  $\beta$ -lactams **5b** and **5e** respectively substituted at C4 by *p*-bromophenyl (**5b**: 54%), or *o*-methoxyphenyl (**5e**: 56%). We have to mention that when a *p*-bromophenyl substituent is present at C4, the cross-coupled product **5b** was obtained along with 17% of debrominated product, but a second cross-coupling did not take place on the aryl group, showing the highly chemoselectivity of the cross-coupling (see SI). Again, the high functional group compatibility was showcased for a *p*-methyl ester substituent, present at C4, affording the corresponding cross-coupled product **5f** and **6b** in 57% yield. As shown for a 3-furyl and a 2-thiophenyl substituent at C4 position of the  $\beta$ -lactam, heterocycles are also tolerated (**6c**: 52% and **6d**: 54%). It is worth mentioning that a similar result was obtained for the cross-coupling of  $\alpha$ -bromo  $\gamma$ -butyrolactam **7a** with diallylzinc (**4**) as the corresponding product **7a4** was isolated in 52% yield.



**Scheme 5.** Cobalt-catalyzed cross-couplings of  $\alpha$ -fluoro  $\alpha$ -bromo  $\beta$ -lactams and  $\alpha$ -bromo  $\beta$ -lactams (top) or **7a** (bottom) with diallylzinc (**4**).

Following up with previous reports on cobalt-catalyzed  $\alpha$ -arylation of  $\alpha$ -bromo amides with Grignard reagents,<sup>[15a, 17]</sup> we were keen to discover whether the conditions for the cobalt-catalyzed cross-coupling with diarylzinc reagents can be applied to  $\alpha$ -bromo carbonyl compounds other than  $\alpha$ -bromo  $\beta$ -lactams e.g. lactams and lactones,  $\alpha$ -bromo amides and  $\alpha$ -bromo esters (Scheme 6). To our delight, the procedure that we have tuned up is broadly applicable to the envisioned substrates affording the cross-coupled products in yields ranging from 53% to 99%.  $\alpha$ -Bromo lactams **7a** and **7b** with different ring sizes,  $\alpha$ -bromo amides (primary bromides **7c–7e**, secondary bromides: **7f–7g** and tertiary bromides **7h**) as well as nitrogen-containing heterocycles were included in our investigations. Pleasingly, the  $\alpha$ -arylation of 5- and 6-membered lactams worked as well as for  $\beta$ -lactams delivering the products **9aa** and **9ba** in 85% and 77% yield, respectively. Comparable results were obtained for primary and secondary  $\alpha$ -bromo amides showing the robustness and the excellent applicability of the coupling (**9ca–9ga**). Even a  $\alpha$ -bromo,  $\alpha,\alpha$ -difluoroamide proved to be a suitable substrate as **9ha** was isolated in 81% yield. Motivated by the robustness of the cross-coupling conditions,  $\alpha$ -bromo lactones (**8a** and **8b**) were subjected to the developed cross-coupling conditions, and **10aa**<sup>[3i]</sup> and **10ab** were obtained in 74% and 85% yield, respectively. Also,  $\alpha$ -bromo esters including an  $\alpha$ -bromo  $\alpha$ -fluoro and an  $\alpha$ -bromo  $\alpha,\alpha$ -difluoro ester were suitable substrates (**8c–8e**) furnishing the cross-coupled products **10ca**, **10da** and **10ea** in satisfying yields ranging from 53% to 61%. It is worth mentioning that  $\alpha$ -bromo lactams **7a** was transformed to **9a** using diallylzinc (**4**) (62%) (Scheme 5).

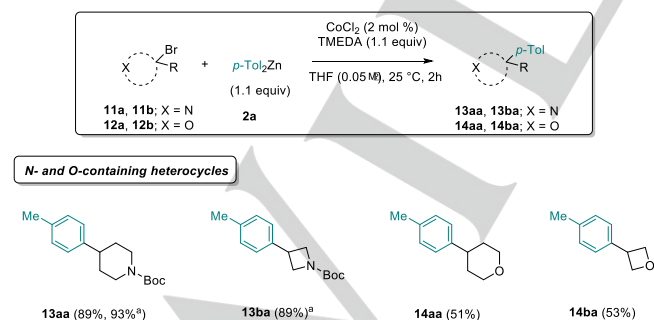




**Scheme 6.** Cobalt-catalyzed cross-coupling of  $\alpha$ -bromo lactams (**7a–7b**), amides (**7c–7h**),  $\alpha$ -bromo lactones (**8a–8b**) and esters (**8c–7e**) with diarylzinc reagents **2a** and **2d**.

Pleasingly, halogeno-substituted nitrogen- and oxygen-containing heterocycles were also suitable substrates (Scheme 7).

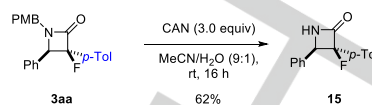
4-Bromo- and 4-iodopiperidine (**11a** and **11a'**), as well as 3-iodo-azetidine (**11b**) were successfully cross-coupled forming **13aa** and **13ba** in high yields. Interestingly, no differences between the 4-bromo- and 4-iodopiperidine were noticed in term of reactivity contrary to the use of Grignard reagents<sup>[15a]</sup>. The same reaction conditions could be also applied to 4-bromo tetrahydropyran and 3-bromo oxetane whereby the corresponding cross-coupled compounds were obtained in 51% and 53% yield, respectively.



**Scheme 7.** Cobalt-catalyzed cross-coupling of bromo *N*-containing and *O*-containing heterocycles with bis(*p*-tolyl)zinc **2a**. a) alkyl iodide was used.

In order to demonstrate that the cross-coupled products **3** can be transformed to a variety of *N*-substituted  $\beta$ -lactams, and in order to have a proof of concept, the *N*-PMB group of **3aa** was

cleaved under oxidative conditions (CAN, MeCN/H<sub>2</sub>O), and **15** was isolated in 62% yield (Scheme 8).



**Scheme 8.** Deprotection of the cross-coupled  $\alpha$ -fluoro  $\beta$ -lactam **3aa**.

## Conclusion

In summary, a convenient, highly efficient and inexpensive cobalt-catalyzed cross-coupling of  $\alpha$ -bromo,  $\alpha$ -fluoro  $\beta$ -lactams with diarylzinc and diallylzinc reagents was developed by utilizing only 2 mol % of CoCl<sub>2</sub>. By using these zinc reagents as cross-coupling partners, a wide array of functional groups, including ester groups, were well-tolerated. As different diarylzinc reagents can be prepared easily, a diversity of substituents at the C3 position of  $\beta$ -lactams could be introduced allowing a fast construction of a  $\beta$ -lactam library. To our delight, the developed protocol showed a great versatility as the reaction conditions could be directly applied to several other carbonyl compounds including  $\alpha$ -bromo lactams and lactones,  $\alpha$ -bromo amides and esters as well as *N*-Boc 4-halogeno piperidines, *N*-Boc 3-iodo azetidines, 4-bromo tetrahydropyran and 3-bromo oxetanes.

## Experimental Section

### General procedure for the cobalt-catalyzed cross-coupling

In a 25 mL round bottom flask,  $\alpha$ -bromo  $\alpha$ -fluoro  $\beta$ -lactam **1** (0.25 mmol, 1.00 equiv) was dissolved in dry THF (at the end, the concentration of **1** is 0.05 M) under an argon atmosphere at rt. CoCl<sub>2</sub> (0.005 mmol, 0.10 mL of 0.05 M solution in THF, 2.0 mol %) and TMEDA (0.275 mmol, 0.40 mL of 0.69 M solution in THF, 1.10 equiv) were added. The zinc reagent **2** or **4** in THF (0.275 mmol, 1.10 equiv) was added over 15 min with a syringe pump. After stirring for 2 h at rt, the reaction was quenched with a saturated aqueous solution of NH<sub>4</sub>Cl (0.30 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (1×30 mL) and then with EtOAc (2×20 mL). The combined organic phases were washed with brine (20 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica gel (*n*-pentane/EtOAc).

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## Authors Contributions

<sup>†</sup> M.M.L. and V.K. contributed equally.

**Keywords:** cross-coupling •  $\beta$ -lactam • cobalt • bis(organo)zinc reagents • catalysis

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## Entry for the Table of Contents

TOC:

A cobalt-catalyzed cross-coupling of  $\alpha$ -bromo carbonyl derivatives and bromo heterocycles with diarylzinc and diarylzinc reagents has revealed to be very chemoselective and general producing the cross-coupled products in good yields

