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Synthetic Methods

Cobalt-Catalyzed Cross-Coupling of 3- and 4-Iodopiperidines with Grignard Reagents

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Abstract: A cobalt-catalyzed cross-coupling between 3- and 4-iodopiperidines and Grignard reagents is disclosed. The reaction is an efficient, cheap, chemoselective, and flexible way to functionalize piperidines. This coupling was used as the key step to realize a short synthesis of (±)-preclamol. Some mechanistic investigations were conducted that highlight the formation of radical intermediates.

Introduction

Myriads of pharmaceuticals and bioactive alkaloids incorporate substituted piperidines.[1] In particular, 4-aryl and 3-aryl piperidines are present in numerous drugs exhibiting a broad spectrum of biological activities (Figure 1). Paroxetine is an antidepressant[2] and naratriptan is used in the treatment of migraine headaches.[3] Preclamol is an antipsychotic drug[4] and MK-4827 inhibits poly(adenosine diphosphate ribose) polymerase, an enzyme responsible for DNA repair that plays a role in several cancers.[5]

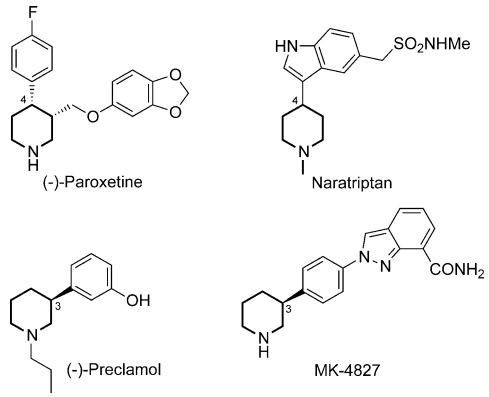
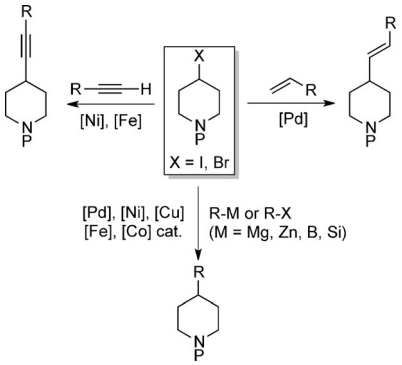


Figure 1. Bioactive 4-aryl and 3-aryl piperidines.

The potent biological activities of substituted piperidines aroused the interest of organic chemists and important efforts have been dedicated to the synthesis of substituted piperidines.[6] Among them, the direct functionalization of the piperidine ring through modular metal-catalyzed cross-couplings appeared as a powerful strategy to generate molecular diversity from halogeno derivatives.[7] Therefore, numerous metal-catalyzed reactions, including Suzuki,[8] Negishi,[9,10] Kumada,[11] Hiyama,[12] Heck,[13] and Sonogashira[14] cross-couplings, have been developed to access 4-alkyl, 4-alkenyl, 4-aryl, and 4-alkynyl piperidines (Scheme 1).[15] Palladium and nickel catalysis rules the field but some examples of iron- and cobalt-catalyzed cross-couplings involving 4-halogeno piperidines have emerged as an attractive alternative due to the cheapness and low toxicity of the metal complexes.[16,17]



Scheme 1. Metal-catalyzed cross-couplings involving 4-halogeno piperidines.

In stark contrast to the functionalization of 4-halogeno piperidines, very few examples of metal-catalyzed cross-couplings on 3-halogeno piperidines have been reported in the literature.[18] 3-Aryl piperidines are generally formed by construction of the ring or by reduction of the corresponding pyridines.[19] In 2013, Baudoin and co-workers described a β-selective arylation of *N*-(*tert*-butoxycarbonyl)piperidines by using a lithiation followed by a transmetallation with zinc and a subsequent Pd-catalyzed Negishi cross-coupling in the presence of an appropriate phosphine ligand (Scheme 2, Eq. (1)).[20] Mo-

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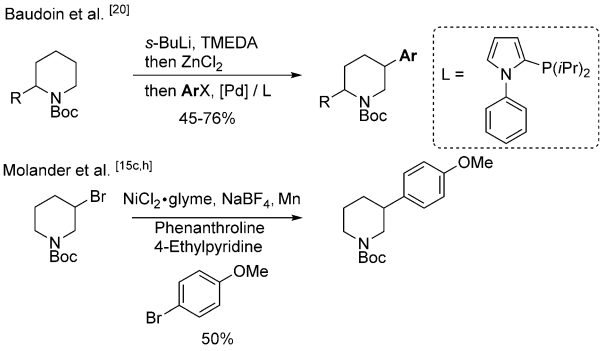
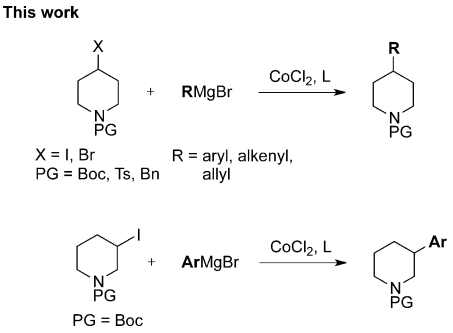
lander et al. developed a nickel-catalyzed reductive cross-coupling between O- and N-heterocyclic bromides or tosylates and (hetero)aryl bromides.[15c,h] A 3-aryl piperidine was obtained from *N*-Boc-3-bromopiperidine with this method, albeit in a moderate 50% yield (Scheme 2, Eq. (2)).



Scheme 2. 3-Arylation of piperidines. Boc = *tert*-butoxycarbonyl; TMEDA = tetramethylethylenediamine.

In the course of our studies toward the development of sustainable synthetic methods to access pharmaceutically relevant scaffolds, we recently developed an iron- and cobalt-catalyzed arylation of saturated N-heterocycles by using Grignard reagents.[21] Notably, a large variety of 4-(hetero)aryl piperidines were prepared through a cobalt-catalyzed cross-coupling. Further studies allowed us to extend the method to the preparation of 4-alkenyl and 4-allyl piperidines. Remarkably, 3-aryl piperidines were synthesized by using a cobalt-catalyzed cross-coupling with Grignard reagents, which constitutes, to the best of our knowledge, the first example of cross-coupling involving a 3-halogeno piperidine and an organometallic reagent. Herein, a full account of our work on the cobalt-catalyzed functionalization of halogeno piperidines is disclosed (Scheme 3).

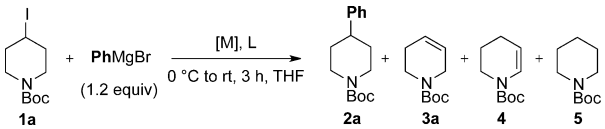


Scheme 3. Functionalization of 4- and 3-halogeno piperidines. Bn = benzyl; PG = protecting group; Ts = toluene-4-sulfonyl.

Results and Discussion

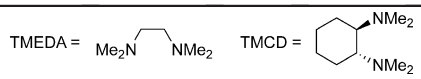
To determine the appropriate catalytic system, the metal-catalyzed cross-coupling between the *N*-Boc-4-iodopiperidine (**1a**) and phenylmagnesium bromide was examined. In the absence of any catalytic system, no reaction occurred (Table 1, entry 1). An iron catalyst was first tested but, when $FeCl_2$ was associated with TMEDA, the cross-coupling product **2a** was formed along with the elimination product **3a** and its isomer **4** in a ratio of 57/28/15 (Table 1, entry 2). The use of (*R*,*R*)-tetramethylcyclohexanediamine (TMCD) instead of TMEDA suppressed the elimination side-products but, in this case, the dehalogenated product **5** was formed and the expected aryl piperidine was isolated in a moderate yield of 60% (Table 1, entry 3). To address these issues, we decided to switch to cobalt catalysis and Co(acetylacetonate)$_3$ (5 mol%), in association with TMEDA (6 mol%), was tested.[22] Pleasingly, even if an incomplete conversion of **1a** was obtained (79%), the side-products **3a**–**5** were not detected (Table 1, entry 4). A switch to TMCD slightly improved the reactivity (Table 1, entry 5) and, finally, the best result was obtained with $CoCl_2$ (5 mol%) and TMCD (6 mol%; Table 1, entry 6).[23] Under these conditions, the iodopiperidine **1a** was fully converted into the cross-coupling product **2a**, which was isolated with a good yield of 81%.

Table 1. Optimization of the catalytic system.

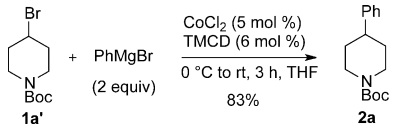


1a **2a** **3a** **4** **5**

Entry	[M] (loading [mol%])	L[a] (loading [mol%])	Conv.[b] [%]	**2a**/**3**/**4**/**5**[c]	Yield of **2a** [%][d]
1	–	–	0	–	–
2	$FeCl_2$ (10)	TMEDA (10)	100	57:28:15:0	n.d.
3	$FeCl_2$ (10)	TMCD (10)	100	87:0:0:13	60
4	$Co(acac)_3$ (5)	TMEDA (6)	79	79:0:0:0	n.d.
5	$Co(acac)_3$ (5)	TMCD (6)	87	87:0:0:0	n.d.
6	$CoCl_2$ (5)	TMCD (6)	100	100:0:0:0	81



4-Bromopiperidine **1a**′ could also be used as the coupling partner under the optimized conditions but, due to its lower reactivity, an increased amount of Grignard reagent was required to reach full conversion (2 equiv versus 1.2 equiv) (Scheme 4).[24]

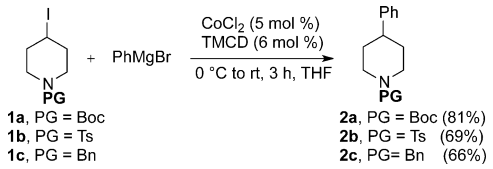


1a' **2a**

Scheme 4. Cross-coupling of 4-bromopiperidine **1a**′.

Recently, the scope of the reaction with the optimized conditions was reported and the N-protecting-group tolerance was first examined.[21] As mentioned before, the reaction was compatible with an *N*-carbamate. An iodosulfonamide was suc-

cessfully involved in the cross-coupling with phenylmagnesium bromide to deliver the aryl piperidine **2b**, albeit with a lower yield than with the *N*-carbamate (69% versus 81%) (Scheme 5). A similar result was obtained in the presence of an *N*-benzyl protecting group (**2c**, 66%).[25]

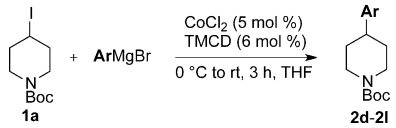


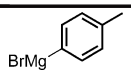
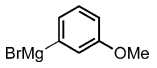
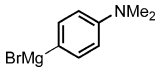
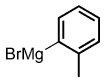
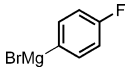
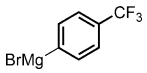
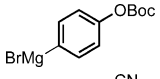
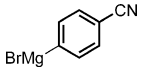
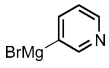
Scheme 5. Compatibility of various N-protecting groups.

The *N*-Boc-4-iodopiperidine (**1a**) was selected for the evaluation of the reactivity of a large variety of aryl magnesium bromides. We had already noticed that the electronic nature of the substituent on the aryl group of the Grignard reagent did not seem to play a significant role in the outcome of the reaction.[21] Indeed, electron-rich aromatic Grignard reagents such as *p*-tolyl- and *m*-OMe-phenylmagnesium bromide were suitable coupling partners and allowed the formation of the corresponding 4-aryl piperidines **2d** and **2e** in excellent yields (81 and 85%, respectively) (Table 2, entries 1 and 2). A *p*-dimethylamino aryl group was also introduced on the piperidine at the C4 position (Table 2, entry 3) and, interestingly, the coupling was not sensitive to steric hindrance because *o*-tolylmagnesium bromide was successfully coupled to the 4-iodopiperidine in 88% yield (Table 2, entry 4). Electron-poor Grignard reagents bearing a *p*-fluoro or a *p*-trifluoro groups were involved in the cross-coupling to provide the desired products in good yields (76 and 96%, respectively) (Table 2, entries 5 and 6).[26] Pleasingly, even the Grignard reagent prepared from *O*-Boc-*p*-bromophenol could be coupled to the 4-iodopiperidine in a satisfying yield (Table 2, entry 7). One limitation was encountered: if a *p*-cyano group was present on the Grignard reagent, the reaction was sluggish and a poor conversion of the starting material (30%) was observed (Table 2, entry 8). This result might be due to a coordination of the nitrile group to the cobalt center that could poison the metal catalyst. In contrast, the use of a heteroaryl Grignard reagent, such as 3-pyridylmagnesium bromide, was tolerated under the optimized conditions. In this case, a decrease in the temperature to −10 °C was beneficial and the coupling product was isolated in an excellent 96% yield (Table 2, entry 9). It is worthy of note that the presence of the basic nitrogen atom does not interfere with the metal catalyst.

Encouraged by these positive results, we then turned our attention to the coupling between 4-iodopiperidines and alkenyl Grignard reagents. With vinylmagnesium bromide, no reaction occurred and the starting material **2a** was fully recovered (Table 3, entry 1). If the *N*-Boc-4-iodopiperidine (**1a**) was treated with isopropenylmagnesium bromide, the expected product **2m** was delivered with a moderate 55% yield (Table 3, entry 2). A similar result was obtained when prop-1-en-1-ylmagnesium bromide (*E*/*Z* = 1/1.5) was used and **2n** was isolated with no significant change in the *E*/*Z* ratio compared to the *E*/*Z* ratio of the Grignard reagent.[29] The use of 2-methyl-1-propenylmagnesium bromide led to the formation of the cross-coupling product **2o** along with the elimination product **3a** in

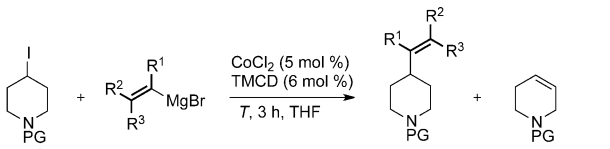
Table 2. Variation of the aryl Grignard reagent.



Entry	ArMgBr[a]	2 (yield [%])
1		**2d** (81)
2		**2e** (85)[21]
3[b]		**2f** (90)[21]
4		**2g** (88)
5		**2h** (76)[21]
6[b]		**2i** (96)[21]
7[b]		**2j** (74)[21]
8[b]		**2k** (n.d.)[21]
9[b]		**2l** (62) (96[c])[21]

[a] 1.2–2 equiv; see the Supporting Information for details. [b] ArMgBr·LiCl prepared by Mg insertion in the presence of LiCl.[27,28] [c] At −10 °C.

Table 3. Cross-coupling with alkenyl Grignard reagents.



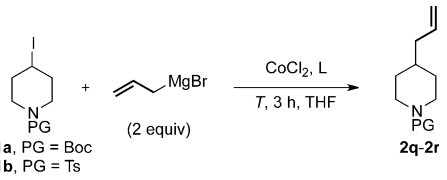
Entry	PG	RMgBr[a]	T [°C]	2/3[b]	2 (yield [%])
1	Boc		0 to RT	–	–
2	Boc		0 to RT	100:0	**2m** (55)
3[c]	Boc		0 to RT	100:0	**2n** (55)[d]
4	Boc		0 to RT	78:22	**2o** (52)
5	Boc		−10	100:0	**2o** (70)
6	Ts		−10	100:0	**2p** (72)

[a] Two equivalents were used. [b] Determined by ^{1}H NMR analysis. [c] *E*/*Z* ratio of the Grignard reagent = 1:1.5. [d] The E/Z ratio was estimated to be 1:1.25.

a 78/22 ratio, which resulted in a moderate yield of **2o** (52%; Table 3, entry 3). Pleasingly, a decrease in the temperature to −10 °C suppressed the undesired elimination process and allowed a significant improvement of the yield of **2o** (70%; Table 3,entry 4). The *N*-carbamate could be changed for an *N*-sulfonamide with no influence on the yield of the cross-coupling (Table 3, entry 5).

To further extend the scope of the cross-coupling, the introduction of an allyl motif on the piperidine ring was investigated. However, if the 4-iodopiperidine **1a** was treated with allyl magnesium bromide in the presence of $CoCl_2$ and TMCD, a low conversion of **1a** into **2q** (23%) was observed and some unidentified impurities were formed (Table 4, entry 1). An increase in the catalytic loading improved the conversion (50%) but, once again, **2q** was obtained together with some impurities (Table 4, entry 2). Inspired by the work of Oshima and coworkers, we switched to another catalytic system composed of $CoCl_2$ (10 mol%) and 1,3-bis(diphenylphosphino)propane (12 mol%).[30] Under these conditions, **2q** was the unique product of the reaction, even if it was isolated in a low 36% yield (Table 4, entry 3). A decrease in the temperature to −10 °C was the key to reach a satisfying yield of 58% and a similar result was obtained at −78 °C (Table 4, entries 4 and 5).[31] Gratifyingly, a switch to a sulfonamide allowed the yield to be improved significantly and **2r** was isolated in 89% yield (Table 4, entry 6).

Table 4. Allylation of 4-iodopiperidines **1a** and **1b**.



1a, PG = Boc
1b, PG = Ts

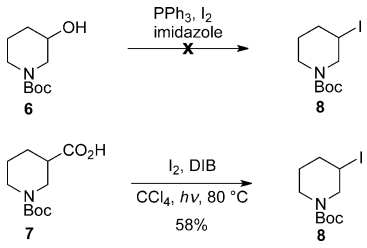
2q-2r

Entry	PG	*T* [°C]	$CoCl_2$ loading [mol%]	L[a] (loading [mol%])	**2** (yield [%])
1	Boc	0 to RT	5	TMCD (6)	**2q** (23)[a]
2	Boc	0 to RT	10	TMCD (12)	**2q** (50)[a]
3	Boc	0 to RT	10	dppp (12)	**2q** (36)
4	Boc	−10	10	dppp (12)	**2q** (58)
5	Boc	−78	10	dppp (12)	**2q** (61)
6	Ts	−10	10	dppp (12)	**2r** (89)[b]

[a] dppp: 1,3-bis(diphenylphosphino)propane. [b] Conversion of **1a** into **2q** was estimated by ^{1}H NMR spectroscopy; some unidentified impurities were observed. [c] A trace of an unidentified impurity was observed.

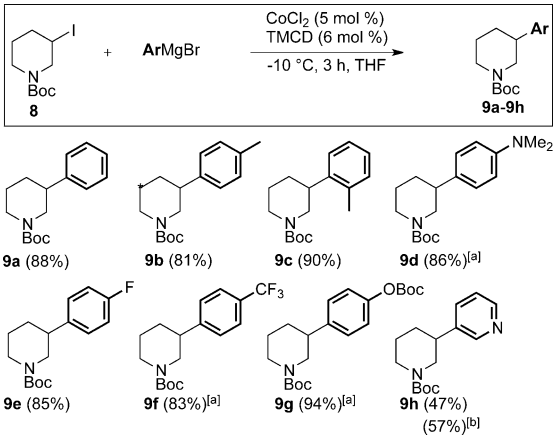
Intrigued by the scarcity of reports on metal-catalyzed cross-couplings involving 3-halogeno piperidines, we then focused on the reactivity of *N*-Boc-3-iodopiperidine in the cross-coupling. The 3-iodopiperidine **8** could not be accessed from the corresponding alcohol **6** and a radical decarboxylation was applied to **7** to overcome this difficulty (Scheme 6). In the presence of iodine and (diacetoxyiodo)benzene under irradiation, **8** was isolated in a moderate yield of 58%.[32]

With the desired substrate in hand, various aryl Grignard reagents were tested under the previous optimized conditions [$CoCl_2$ (5 mol%), TMCD (6 mol%)]. It was essential to perform



Scheme 6. Synthesis of *N*-Boc-3-iodopiperidine (**8**). DIB = (diacetoxyiodo)benzene.

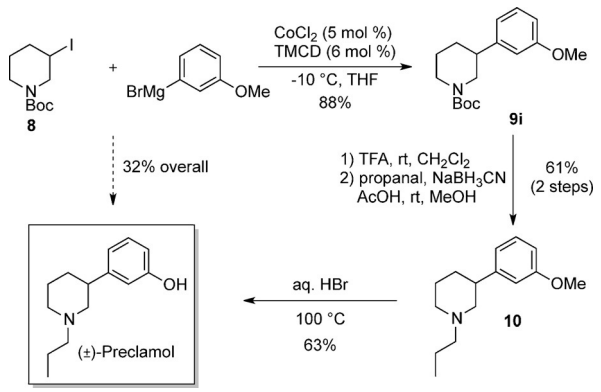
the reactions at −10 °C to reach high yields in the coupling products and excellent yields, of up to 94%, were obtained for the formation of the desired compounds. A wide range of aryl Grignard reagents were successfully coupled to the 3-iodopiperidine, irrespective of the electronic nature of the substituents on the aryl group (Scheme 7). The tolerance of some functional groups, such as a Boc-protected phenol, under the reaction conditions offers the opportunity for further transformations. If a Grignard reagent possessing a pyridyl ring was involved, a moderate yield of 47% of **9h** was obtained in the presence of 6 mol% of TMCD. An increase in the catalytic loading of TMCD to 50 mol% allowed the yield to be improved to 57%.



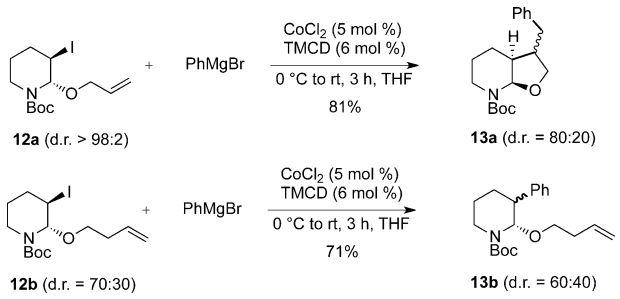
Scheme 7. Cross-coupling involving 3-iodopiperidine **8**. [a] Grignard prepared as ArMgBr·LiCl.[29] [b] Using 50 mol% of TMCD.

The coupling method was successfully applied to a short synthesis of (±)-preclamol (Scheme 8).[33] The *N*-Boc-3-iodopiperidine (**8**) was first coupled with 3-methoxyphenylmagnesium bromide to give **9i** (88%). The propyl substituent on the nitrogen atom was then introduced by treatment with trifluoroacetic acid followed by a reductive amination with propanal. Finally, the cleavage of the methoxy ether in the presence of HBr delivered (±)-preclamol (32% overall yield). This sequence illustrates the great potential of our coupling method in the synthesis of pharmaceutically relevant molecules.

The mechanism of the cobalt-catalyzed cross-coupling has not been fully elucidated yet; however, the formation of radical

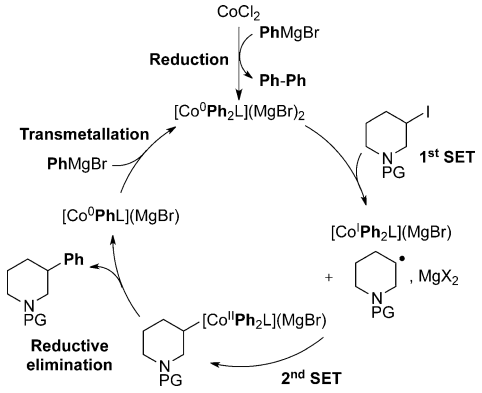


Scheme 8. Synthesis of (±)-preclamol. TFA = trifluoroacetic acid.



Scheme 10. Cross-couplings involving radical clocks **12a** and **12b**.

intermediates has been demonstrated on several occasions.[34] According to literature reports, it can be proposed that, after the reduction of $CoCl_2$ into an active Co(0) catalyst by the Grignard reagent, a first single-electron transfer (SET) occurs to release a radical intermediate. A second SET completes the formal oxidative addition of the cobalt atom into the C–I bond. Finally, a reductive elimination furnishes the coupled product and a transmetallation with PhMgBr releases the active catalyst (Scheme 9).



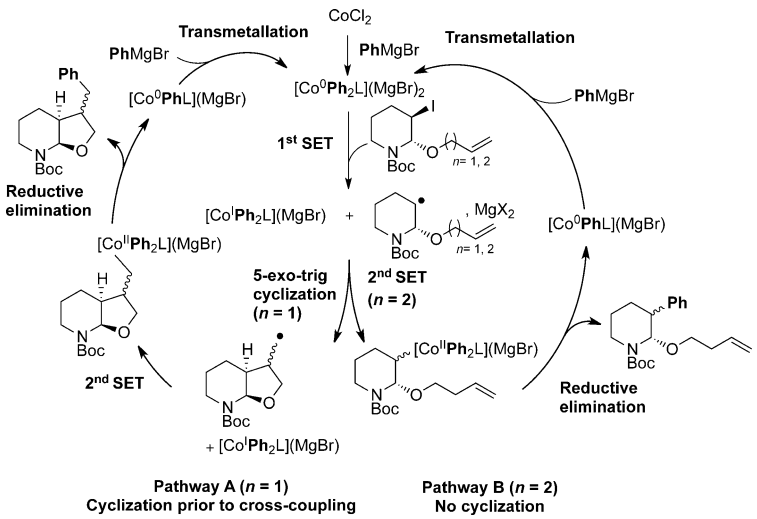
Scheme 9. Hypothetical mechanism for the Co-catalyzed cross-coupling. SET: single-electron transfer.

To support the hypothesis of radical-intermediate formation, the two radical clocks **12a** and **12b** were prepared[35] and involved in Co-catalyzed cross-coupling with phenylmagnesium bromide (Scheme 10). When **12a** was treated with phenylmagnesium bromide in the presence of the optimized catalytic system, the bicyclic product **13a**, which results from a 5-*exo-trig* cyclization prior to the cross-coupling, was formed exclusively. By contrast, the use of **12b**, which bears an additional carbon atom on the ether pendant chain, only led to the disubstituted piperidine **13b**.

The apparently opposite results obtained with radical clocks **12a** and **12b** might be explained by kinetic considerations relative to the step subsequent to the first SET. The 5-*exo-trig* cyclization is approximately 1000 times faster than the 6-*exo-trig* cyclization. As a consequence, in the case of **12a**, the cyclization is fast enough to occur before the cross-coupling (Scheme 11, Pathway A), whereas the cross-coupling is faster than the cyclization step for **12b** (Scheme 11, Pathway B). In both pathways, a final reductive elimination provided the product and a subsequent transmetallation afforded the active catalyst.

Conclusion

In summary, an efficient, chemoselective, cheap, and convenient cobalt-catalyzed cross-coupling between iodopiperidines and Grignard reagents was developed. The reaction is general because 4-iodo- as well as 3-iodopiperidines were functionalized with a wide range of Grignard reagents, including aryl, alkenyl, and allyl Grignard reagents. The reactions generally proceed with high yields and are compatible with several functionalized groups, such as carbamates, ethers, and pyridine; the reaction thus offers a large modularity. To the best of our knowledge, this constitutes the first example of metal-catalyzed cross-coupling between a 3-halogeno piperidine and an organometallic partner. The method could be of high synthetic value to prepare biologically active compounds incorporating



Scheme 11. Hypothetical mechanism with radical clocks **12a** and **12b**.

piperidine scaffolds, as was demonstrated through the short synthesis of (±)-preclamol with a cross-coupling as the key step. With consideration of the various pharmaceutical properties of numerous piperidine-containing molecules, this cross-coupling could become a powerful tool in drug discovery.

Experimental Section

General procedure for the cobalt-catalyzed cross-coupling

$CoCl_2$ (5 mol%) and TMCD (6 mol%) were added to a solution of the halogeno piperidine (1 equiv). The Grignard reagent (1.2–2 equiv) was then added dropwise (no need for a syringe pump) at the appropriate temperature and the resulting mixture was stirred for 3 h at the appropriate temperature. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$ and filtered, then the solvent was removed under vacuum. Flash chromatography afforded the expected cross-coupling product.

Keywords: catalysis · cobalt · cross-coupling · piperidines · synthetic methods

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[25] When the *N*-Ts-iodopiperidine and the *N*-Bn-iodopiperidine were used, two equivalents of Grignard reagent were required. In the case of the *N*-Bn-iodopiperidine, TMCD was used at a loading of 50 mol%.

[26] A cross-coupling between bromide derivative **1a'** and the 4-trifluoromethylphenylmagnesium bromide reagent (2 equiv) was carried out and led to incomplete conversion of **1a'** (42%, estimated from the ^{1}H NMR spectra of the crude mixture), which confirmed that iodide derivatives are more reactive.

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