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Introduction of cyclopropyl and cyclobutyl ring on alkyl iodides through cobalt-catalyzed cross-coupling

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Supporting Information Placeholder

ABSTRACT: A cobalt-catalyzed cross-coupling between alkyl iodides and cyclopropyl, cyclobutyl and alkenyl Grignard reagents is disclosed. The reaction allows the introduction of strained rings on a large panel of primary and secondary alkyl iodides. The catalytic system is simple, non-expensive and the reaction is general, chemoselective and diastereoconvergent. The alkene resulting from the cross-coupling can be transformed to substituted cyclopropanes using a Simmons-Smith reaction. The formation of radical intermediates during the coupling is hypothesized.

Since the isolation of (+)-*trans*-chrysanthemic acid,¹ a myriad of cyclopropane-containing natural products has been extracted from diverse sources such as fungi, plants, marine organisms or microorganisms.² The rigidity of the cycle, its ring strain associated to its three dimensionality notably raised the attention of medicinal chemists and, since the 1960s, cyclopropanes have been introduced in a wide variety of pharmaceutically active compounds.^{3,4} Particularly, the identification of cyclopropanes as excellent surrogates of phenyl ring in bioactive molecules was an important breakthrough in drug design.^{5,6} Cyclobutanes are less popular than cyclopropanes but their presence in bioactive natural products⁷ as well as the need for an exploration of the chemical space in drug design motivate an increasing interest for this cycle. Thus, a large diversity of methods including ring-closure reactions, rearrangements, pericyclic reactions and carbenoid reactions has been developed to access either cyclopropanes or cyclobutanes.^{3,7,8} All these reactions involve the formation of the ring but the direct introduction of a pre-existing carbocycle is an alternative attractive strategy. With this idea in mind, metal-catalyzed cross-coupling reactions between a halide and an organometallic reagent featuring the strained cycle have been considered.^{9,10} Alkyl halides are often considered as challenging partners in cross-coupling reactions due to β -elimination or dehalogenation side-reactions. As a result, most of the existing Kumada,¹¹ Suzuki¹² or Negishi¹³ coupling between cyclopropyl/cyclobutyl organometallics and alkyl halides are limited to activated allylic or benzylic halides (Scheme 1, eq. 1). To date, only copper- and iron-catalyzed cross-couplings allowed the introduction of cyclopropyl/cyclobutyl rings on unactivated alkyl halides

albeit with a restriction to primary alkyl halides (Scheme 1, eq. 2).^{14,15,16} To the best of our knowledge, a single example of cyclopropanation of a secondary unactivated alkyl chloride has been reported using a Ni-catalyzed Suzuki-type cross-coupling (Scheme 1, eq. 3).¹⁷

Scheme 1. Introduction of cyclopropyl and cyclobutyl rings through metal-catalyzed cross-coupling.

Previous work

This work

Over the past decades, cobalt-catalyzed cross-coupling has emerged as a powerful tool, especially enabling the extensive use of alkyl halides as partners.^{18,19} In the course of our studies towards the development of sustainable cross-coupling reactions,²⁰ the cobalt-catalyzed alkylation of cyclopropyl- and cyclobutylmagnesium bromides with alkyl halides was developed. The method allows the facile and direct introduction of the strained carbocycles on a variety of primary and secondary alkyl halides including molecules featuring attractive scaffolds such as *N*-heterocycles. It was extended to alkenyl Grignard reagents as the resulting alkenes could be further transformed to cyclopropanes (Scheme 1, eq. 4).

The reaction between the primary alkyl iodide **1.1** and cyclopropylmagnesium bromide was first examined. Investigations were conducted to identify the best conditions for the cross-coupling and a range of ligands, catalysts, temperature, solvents and addition speed and were screened. Only the key facts of this optimization study are reported below.²¹ Besides the desired cross-coupling product **2.1**, several by-products could be formed during the reaction such as the terminal alkene **3.1** resulting from an elimination, the internal alkene **4.1** obtained after the double bond migration of **3.1** or the dehalogenated product **5.1**.²² Based on our experience, we first selected CoCl₂ (10 mol %) as a catalyst associated to a diamine ligand (20 mol %). With (*R,R*)-tetramethylcyclohexanediamine (TMCD), the coupling product was obtained in a moderate yield of 42% due to an important simultaneous formation of side-products **4.1** and **5.1** (Table 1, entry 1). Using tetramethylethylenediamine (TMEDA) slightly improved the selectivity of the reaction toward the formation of **2.1** (Table 1, entry 2). Phosphine ligands were tested delivering traces or small amount of **2.1**, the best results being obtained with triphenylphosphine (Table 1, entry 3). TMEDA was thus selected and a decrease of the temperature was envisioned to improve the selectivity. Indeed, working at 0 °C contributed to reduce the alkenes formation, furnishing **2.1** in 69% yield (Table 1, entry 4). However, reducing the temperature at -25 °C did not allow to suppress the elimination and affected the conversion of the iodide (Table 1, entry 5). The addition rate of the Grignard reagent was identified as a significant parameter and using a syringe pump (*v* = 0.52 mmol.h⁻¹) proved beneficial to the selectivity and reproducibility of the reaction (Table 1, entry 6). Pleasingly, the catalytic loading could be reduced to 3.5 mol % for both the cobalt salt and TMEDA (Table 1, entry 7) and when CoCl₂ was changed for the non-hygroscopic Co(acac)₃, the coupling product was obtained with a good yield of 80% (Table 1, entry 8). However, during the course of our studies, the introduction of 1 equiv of TMEDA appeared crucial to ensure the generality of the reaction and, under these conditions, iodide **1.1** was efficiently transformed to **2.1** (84%) (Table 1, entry 9).^{23,24}

Table 1. Optimization of the reaction conditions.

entry	[Co] (mol %)	L (mol %)	T °C	2.1 ^[a] (%)	3.1 + 4.1 ^[a] (%)	5.1 ^[a] (%)
1	CoCl ₂ (10)	TMCD (20)	rt	42	28	11
2	CoCl ₂ (10)	TMEDA (20)	rt	56	17	< 5
3	CoCl ₂ (10)	PPh ₃ (20)	rt	28	24	6
4	CoCl ₂ (10)	TMEDA (20)	0	69	6	< 5
5 ^[b]	CoCl ₂ (10)	TMEDA (20)	-25	37	14	6
6 ^[c]	CoCl ₂ (10)	TMEDA (20)	0	76	< 5	< 5
7 ^[c]	CoCl ₂ (3.5)	TMEDA (3.5)	0	73	5	< 5
8 ^[c]	Co(acac) ₃ (3.5)	TMEDA (3.5)	0	80	< 5	< 5
9 ^[c]	Co(acac) ₃ (3.5)	TMEDA (100)	0	84	< 5	< 5

[a] Yields were calculated from the ¹H NMR spectrum of the mixture of **2-5** obtained after flash column chromatography. [b] Unreacted iodide **1.1** was observed (13%). [c] Slow addition of the Grignard reagent (0.52 mmol.h⁻¹).

With the optimized conditions in hand, the scope of the reaction was examined and a range of primary iodides was first evaluated.²⁵ The presence of a protected alcohol, either as a benzyl ether or as a silyl ether, on the alkyl iodide was well tolerated and the corresponding coupling products were formed in good yields (86% and 89% respectively). When an alkyl iodide bearing an aryl bromide was involved in the cross-coupling, a selective introduction of the cyclopropyl group on the alkyl chain was observed and **2.4** was obtained with a 78% yield. This chemoselectivity towards alkyl iodides allows the use of polyfunctional molecules, offering opportunities for further functionalization. When a cyano group was present on the alkyl iodide, a significant drop in yield of the coupling product was observed (31%), mainly due to the undesired addition of the Grignard reagent on the electrophilic nitrile moiety. The steric hindrance induced by a gem-dimethyl group could suppress this side reaction allowing the coupling to proceed with high chemoselectivity (**2.6**, 81%). Pleasingly, an ester group was also compatible with the reaction conditions as **2.7** was isolated in 56% yield with no contamination by elimination or dehalogenation side products (Scheme 2).²⁶

Scheme 2. Cross-coupling between cyclopropyl magnesium bromide and primary alkyl iodides.

Some of the so-formed alkenes could then be involved in a Simmons-Smith type reaction to afford polysubstituted cyclopropanes (Scheme 7).

Scheme 7. Cyclopropanation of alkenes 6.1-6.3.

Finally, the coupling was extended to the introduction of a cyclobutane moiety on alkyl iodides. Good yields in the coupling products were obtained with primary and secondary alkyl iodides including iodo *N*-heterocycles (Scheme 8).²⁵ To the best of our knowledge, this reaction is the first example of cyclobutyl ring introduction on a secondary alkyl halide through a metal-catalyzed cross-coupling.

Scheme 8. Co-catalyzed cross-coupling between halides and cyclobutylmagnesium bromide.

In summary, we developed a flexible, efficient and cost-effective cross-coupling allowing the introduction of cyclopropyl, cyclobutyl and alkenyl moieties on both primary and secondary alkyl iodides. The reaction tolerated an array of functional groups and was applied to the functionalization of *N*-heterocycles, which are valuable scaffolds in pharmaceutical industry. To the best of our knowledge, this is the first general cross-coupling of cyclopropyl and cyclobutyl magnesium bromides with alkyl iodides including secondary iodides. In addition, alkenyl Grignard reagents are also suitable partners resulting in the corresponding alkenes that can be transformed into polysubstituted cyclopropanes. The formation of radical intermediates could be hypothesized and could explain the diastereomeric convergence of the coupling. This cross-coupling appears as a promising method for the late-stage introduction of cyclopropyl or cyclobutyl rings and could thus become an attractive tool for the design and synthesis of bioactive molecules for medicinal chemists.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no conflict of interests.

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²¹ For the whole optimization study, see the Supporting Information.

²² Compounds **2.1**, **3.1**, **4.1** and **5.1** could not be separated by flash chromatography on silica gel. The indicated yields were calculated from the ¹H NMR spectrum of the mixture **2-5** obtained after purification.

²³ Primary bromides revealed less reactive than iodides under the optimized conditions and stirring the reaction at rt for 1 h was necessary to ensure full conversion of the starting material, which led to the coupling product in moderate yield (45%).

²⁴ When the reaction was conducted on 1 mmol of **1.1**, the coupling product was isolated with a good yield of 87% and no trace of by-products was detected. The reaction was also carried out on 3.6 mmol of **1.1** (1 g)

and the coupling product was obtained with a yield of 82% contaminated by 2% of dehalogenated product, see the Supporting Information for details. The rate of addition of the Grignard reagent can be increased to 26 mmol/h, providing the coupling product in 80% yield contaminated by 9% of side-products.

²⁵ In some cases, the coupling products were isolated together with a small amount of elimination and/or dehalogenation products (<7%) that could not be separated by flash chromatography, see Supporting Information for details.

²⁶ The tertiary alcohol resulting from a bis-addition of the Grignard reagent on the ester was also isolated (5% yield). When a catalytic amount of LiI (7 mol %) was added to the catalytic system [Co(acac)₃ (3.5 mol %), TMEDA (3.5 mol %)] an improved yield (71%) in **2.7** was obtained. The effect of LiI is not fully understood.

²⁷ The coupling product **2.8** was isolated together with dehalogenation and elimination products (38%).

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²⁹ The cross-coupling between iodide **1.1** and cyclopropylmagnesium bromide was performed under the optimized conditions in the presence of 1 equiv of (*E*)-stilbene as a radical scavenger. The addition of (*E*)-stilbene showed no significant effect on the outcome of the reaction (71% yield in **2.1**) and no adduct resulting from a radical attack on the activated olefin could be detected. This result could be explained by kinetic reasons, the recombination of the radical with the metal complex being faster than the intermolecular reaction.

³⁰ For examples of Co-catalyzed alkenylation of alkyl halides, see: 19a, 19b.

³¹ Cross-coupling product **6.2** was isolated together with 13% of dehalogenation and elimination products.