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Rh-Catalyzed C–H alkylation enabling modular synthesis of CF_3-substituted benzannulated macrocyclic inhibitors of B cell responses†

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Inspired by aspirin and chalcone, herein, we describe a modular biomimetic strategy to achieve a new class of CF_3-bearing benzannulated macrolactams. The key to the success of macrolactams was the utilization of a highly chemoselective Rh(III)-catalyzed native carboxylic acid-directed C–H alkylation. Moreover, the unique CF_3-containing benzannulated macrocycles showed decent immunosuppressive effects on B cells *in vitro*, including proliferation, activation, and antibody production upon specific stimulation implicating TLR and BCR signaling.

Recently, increasing attention has been paid to natural macrocyclic small molecules; not only have they become efficient probes for challenging target validation, but they have also emerged as powerful candidates to interfere in protein–protein interactions.[1] In particular, benzannulated macrocycles are of great interest due to their diverse and interesting biological activities such as anti-cancer, anti-HIV, and immunosuppressive activities (Fig. 1A).[2] Despite the attractive characteristics offered by natural benzannulated macrocyclic molecules, their sustainability could be hampered by gene expression limitation of microbes or plants and difficulty of resupply. Therefore, the development of new strategies and methods to access natural macrocycle-like compounds with a broader chemical space still represents an important goal in organic synthesis.[3] In this field, Spring and coworkers[4] developed an advanced build/couple/pair (B/C/P)-based strategy based on a pioneering concept from Schreiber[5] to generate a variety of macrocycle libraries. The state of the art in the B/C/P strategy is that the use of C is mainly limited to the traditional chemical reactions. While the B/C/P strategy could yield structurally diverse macrocycle collections, the chemical space of macrocycles still cannot satisfy the biological space. Therefore, the solution for this challenge is to develop new types of chemical coupling reactions.[6] Additionally, incorporation of natural privileged structures into macrocyclic scaffolds could offer an efficient way to enhance the biological performance and drug-likeness of the molecules.[7] For example, Lubell and Ong used endogenous growth hormone-releasing peptide 6 (GHRP-6) as a natural building block and successfully constructed a series of azapeptide macrocycles which exhibited unprecedented affinity for the CD-36 receptor.[7a] Very recently, Liu and co-workers discovered a highly potent macrocyclic inhibitor for hENT1 by merging the optimized FKBP-binding domains derived from rapamycin and various peptides.[7b]

Trifluoromethyl groups ($-CF_3$) are one of the most frequently encountered motifs in drug molecules because of their profound modifications of biological activities and physical properties, such as metabolic stability, lipophilicity, and permeability.[8] Thus, the construction of various CF_3-bearing molecules has attracted considerable interest, and impressive achievements have been made in the past few decades.[9]

Inspired by natural products and owing to our interest in developing new coupling reactions,[10] we set out to create $C(sp^3)$-rich CF_3-bearing benzannulated macrolactams *via* a short and modular biomimetic strategy, which utilizes natural analogs as building blocks. Notably, among the CF_3-containing molecule libraries, the accessibility of structurally diverse $C(sp^3)$-rich CF_3-containing macrocyclic compounds is extremely limited.[11] In this regard, we questioned whether successive and concise C–H alkylation and amidation can be applied to assemble these building blocks faithfully into the target CF_3-bearing macrolactams. The successful development of these processes would require: (i) the conditions for C–H alkylation that can promote chemoselective C–C bond formation

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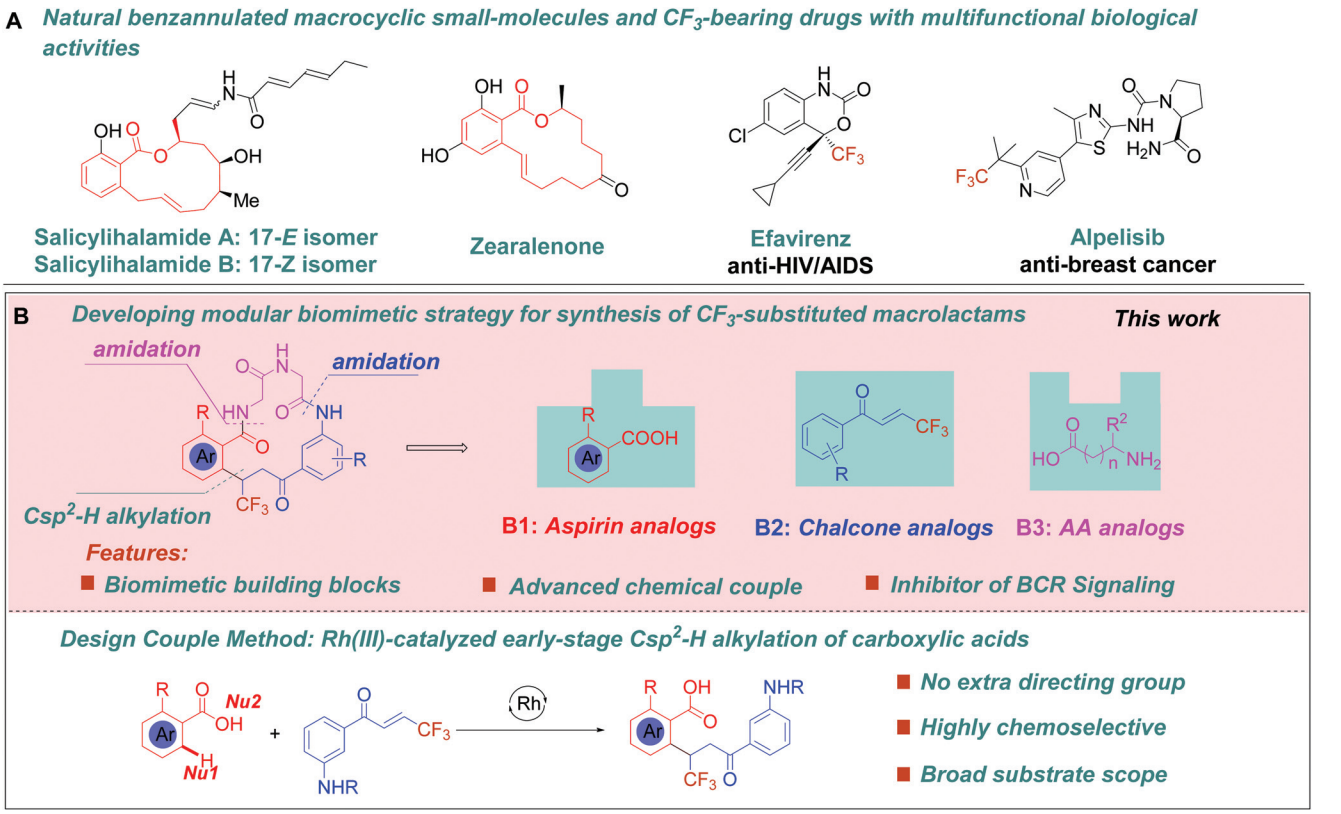
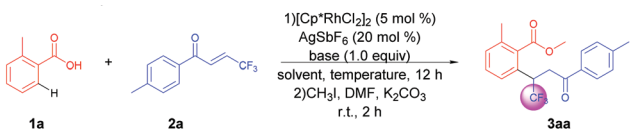


Fig. 1 (A) Natural benzannulated macrocyclic small molecules and CF_3-bearing drugs with multifunctional biological activities. (B) Developing a biomimetic B/C/P strategy for the synthesis of CF_3-substituted macrolactams enabled by Rh(III)-catalyzed Csp^2–H alkylation of carboxylic acid.

Table 1 Optimization of reaction conditions[a]



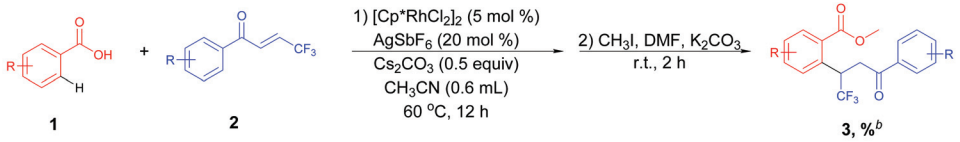
Entry	Solvent	Base	t (°C)	Yield[b] (%)
1	Toluene	K_2CO_3	80	41
2	DCE	K_2CO_3	80	39
3	CH_3CN	K_2CO_3	80	58
4	1,4-Dioxane	K_2CO_3	80	62
5	THF	K_2CO_3	80	46
6	TFE	K_2CO_3	80	50
7	1,4-Dioxane	No base	80	15
8	1,4-Dioxane	K_3PO_4	80	50
9	1,4-Dioxane	KOAc	80	39
10	1,4-Dioxane	K_2CO_3	60	66
11	1,4-Dioxane	Cs_2CO_3	60	69
12	CH_3CN	Cs_2CO_3	60	72
13[c]	**CH_3CN**	**Cs_2CO_3**	**60**	**80 (82)**

[a] Reaction conditions: (1) **1a** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), base (1.0 equiv.), solvent (1.0 mL) at 80 °C under air for 12 h; (2) CH_3I (3.0 equiv.), K_2CO_3 (1.0 equiv.), DMF (1 mL) at r.t. under air for 2 h. [b] Yields were determined by ^1H NMR using CH_2Br_2 as the internal standard; the isolated yield is given in parentheses. [c] (1) Cs_2CO_3 (0.5 equiv.), CH_3CN (0.6 mL) at 60 °C under air for 12 h; (2) CH_3I (3.0 equiv.), K_2CO_3 (1.0 equiv.), DMF (1 mL) at r.t. under air for 2 h.

and (ii) catalysts that can overcome the complications between β-H elimination and protonation from the alkyl-Rh(III) species and retain the C(sp^3)-rich center.

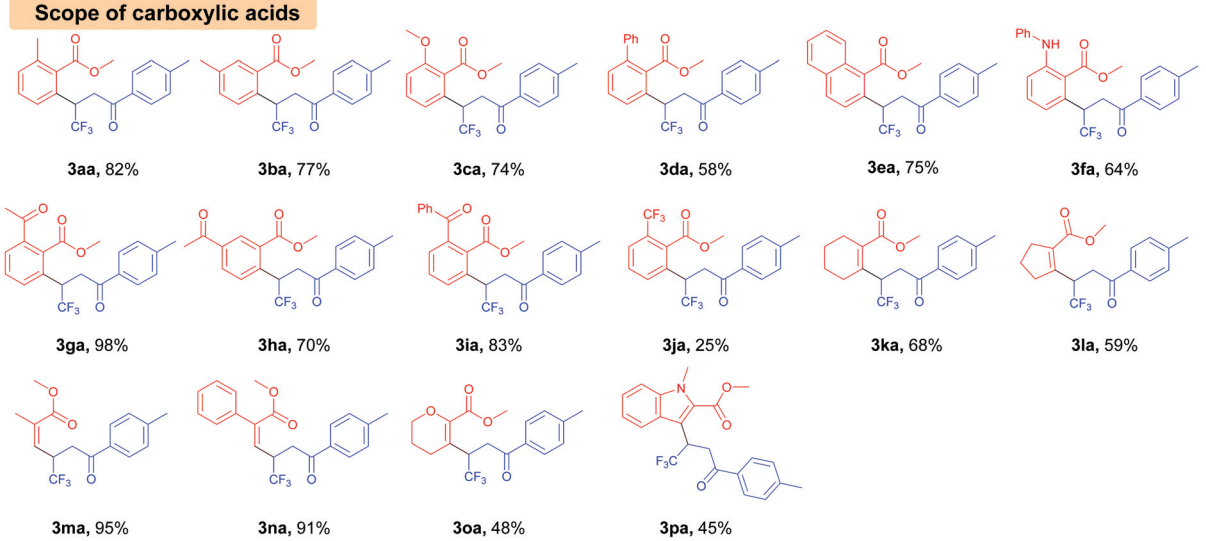
Herein, we detail the successful realization of these ideas through the development of a biomimetic B/C/P strategy for the synthesis of C(sp^3)-rich CF_3-bearing benzannulated macrolactams (Fig. 1B). The collected macrolactams employs readily available aspirin, chalcone, and amino acid (AA) analogs as building blocks, and the key step is enabled by Rh(III)-catalyzed native carboxylic acid-directed C–H alkylation.[12] Moreover, a high-throughput bioactive screening revealed that these unique macrolactams showed inhibition of B cells *in vitro*, including proliferation, activation, and antibody production upon specific stimulation implicating TLR and BCR signaling.

Table 2 Substrate scopes[a]



1 2 3, %[b]

Scope of carboxylic acids

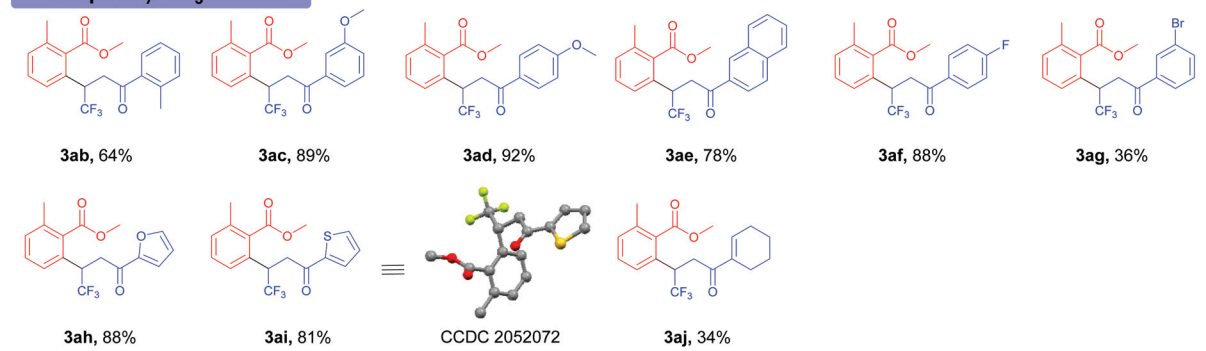


3aa, 82% **3ba**, 77% **3ca**, 74% **3da**, 58% **3ea**, 75% **3fa**, 64%

3ga, 98% **3ha**, 70% **3ia**, 83% **3ja**, 25% **3ka**, 68% **3la**, 59%

3ma, 95% **3na**, 91% **3oa**, 48% **3pa**, 45%

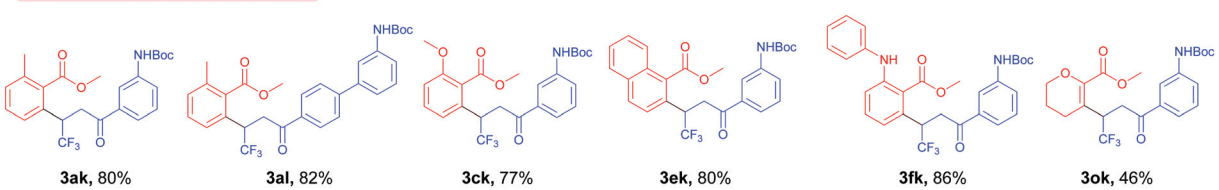
Scope of β-CF_3-enones



3ab, 64% **3ac**, 89% **3ad**, 92% **3ae**, 78% **3af**, 88% **3ag**, 36%

3ah, 88% **3ai**, 81% CCDC 2052072 **3aj**, 34%

Sensitive functional group



3ak, 80% **3al**, 82% **3ck**, 77% **3ek**, 80% **3fk**, 86% **3ok**, 46%

[a] Standard conditions: (1) **1a** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Cs_2CO_3 (0.5 equiv.), CH_3CN (0.6 mL) at 60 °C under air for 12 h; (2) CH_3I (3.0 equiv.), K_2CO_3 (1.0 equiv.), DMF (1 mL) at r.t. under air for 2 h. [b] Isolated yield.

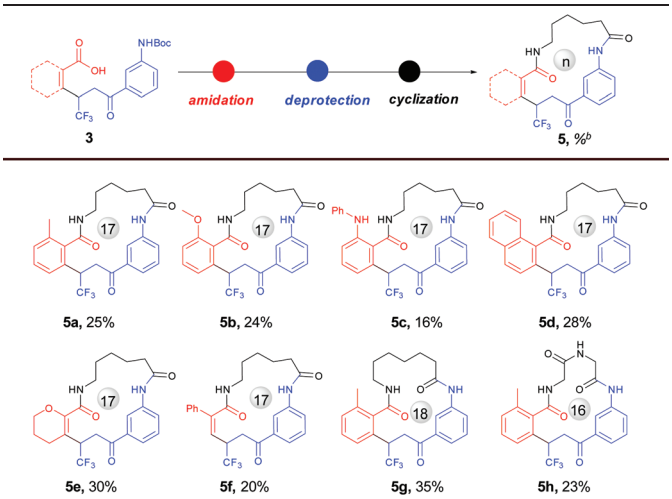
To test this hypothesis, we commenced our building block assembly by designing the C–H alkylation of 2-methylbenzoic acid **1a** with (*E*)-4,4,4-trifluoro-1-(*p*-tolyl)but-2-en-1-one **2a** as the CF_3-containing reagent. Initially, the nucleophilic addition of the hydroxyl group (–OH) to **2a** was assumed to take place preferentially, owing to its weaker bond-dissociation energy (BDE) and better nucleophilic character compared to the C(sp^2)–H bond. Unexpectedly, the chemoselectivity was reversed and the C–H alkylation product **3aa** was exclusively achieved in a 41% isolated yield by using 5 mol% of $[Cp^*RhCl_2]_2$ and 20 mol% of $AgSbF_6$ in toluene at 80 °C and in the presence of 1.0 equiv. of K_2CO_3 as a base (Table 1, entry 1). This reverse chemoselectivity offers a fundamental assurance for the successful construction of C(sp^3)-rich CF_3-containing macrocyclic targets. Further optimization of solvents showed that the use of CH_3CN and 1,4-dioxane promoted the efficiency and provided the product **3aa** in 58% and 62% yields, respectively (Table 1, entries 3 and 4). Normally, the addition of a base is found to be crucial for the carboxylic acid-directed C–H activation; we therefore set out to test a variety of bases commonly used in such reactions. Indeed, without a base, the reaction efficiency decreased sharply, giving only 15% yield of **3aa** (Table 1, entry 7). When the reaction was performed in the presence of Cs_2CO_3, the reaction efficiency was increased significantly and it could afford **3aa** in 69% NMR yield. Gratifyingly, decreasing the temperature to 60 °C and reducing the amount of the base loading to 0.5 equiv. gave **3aa** in 82% isolated yield (Table 1, entry 13).

Considering the follow-up structure–activity relationship (SAR) investigation, with the optimal conditions in hand, we next examined the substrate scope of this Rh(III)-catalyzed C–H alkylation. As shown in Table 2, our developed protocol was applicable to a variety of benzonic acids regardless of the electronic and steric properties of the substituents on the benzene ring (**3aa–3da**, **3fa–3ja**). Additionally, the aryl ring could be replaced by a naphthyl ring (**3ea**) without an obvious erosive effect on reaction efficiency. Besides benzonic acids, we were delighted to find that α,β-unsaturated carboxylic acids, which are rarely reported in directing vinylic C–H bond alkylation, could react smoothly with **2a**, furnishing the desired products in satisfactory yields (**3ka–3oa**). Gratifyingly, the reaction was also compatible with indole carboxylic acid (**3pa**), which is commonly encountered in drug design, because of its unique biological properties. Furthermore, a range of β-trifluoromethyl-α,β-unsaturated ketones bearing electron-donating as well as electron-withdrawing groups at the *ortho* (**3ab**), *meta* (**3ac**, **3ag**) and *para* (**3ad**, **3af**) positions of the aryl ring were amenable to this reaction and delivered the corresponding products in good yields. Although the bromo-substituted substrate only afforded the product **3ag** in 36% yield, it could open possibilities for downstream modification through orthogonal cross-coupling chemistry. Naphthalene-containing β-trifluoromethyl-α,β-unsaturated ketones delivered the product **3ae** in 78% yield. It is worth mentioning that furan (**3ah**) and thiophene (**3ai**) heterocycles could also be incorporated with very good yields. A safe assignment of the structure **3ai** was unambiguously validated by single-crystal X-ray analysis. However, the introduction of nonaromatic cyclohexene on the substrate greatly reduced the reactivity and offered the corresponding product (**3aj**) in 34% yield. Notably, the sensitive functional group –NHBoc worked well to give the desired products in good yields (**3ak**, **3al**, **3ck**, **3ek**, **3fk**, **3ok**, 46–86%), which provided an important handle for the subsequent macrocyclization.

Very recently, we have successfully used long-chain amino acids to assemble macrolactams, which efficiently inhibited *P*-glycoprotein[10g] and showed significant anti-inflammatory activities against TNF-α, IL-6, and IL-1β.[10i] We speculated that these long-chain amino acids could change the conformation of macrolactams and make the ring not rigid. Encouraged by these results, we attempted to test the generality of long-chain amino acids in other macrocycles. Generally, a series of C(sp^3)-rich CF_3-bearing macrolactams were obtained in synthetically useful yields after four steps by a biomimetic modularization strategy (Table 3). Importantly, the linear substrates containing the α,β-unsaturated motifs tethered with ε-amino acid could be cyclized smoothly to yield 17-membered macrocycles **5e** and **5f** in 30% and 20% yields, respectively. In the context of drug discovery, peptides are particularly interesting owing to their increased hydrogen bond interaction. Accordingly, we challenged our method by introducing natural amino acids in the substrate for macrocyclization. We were delighted to observe that the 16-membered compound **5h** featuring a dipeptide backbone could be readily isolated in 23% yield.

To explore whether these CF_3-bearing benzannulated macrolactams obtained by a modular biomimetic strategy could successfully exhibit pharmacologically relevant features,

Table 3 Construction of functional CF_3-substituted benzannulated macrolactams by a biomimetic B/C/P strategy[a]



[a] Standard conditions: (1) amidation: **3** (0.3 mmol), amino acid esters (0.45 mmol), EDCI (1.2 equiv.), HOBt (1.5 equiv.), Et_3N (4.5 equiv.), DMF (3 mL) at r.t. under air for 12 h; (2) deprotection: (a) CH_3OH/THF/H_2O (1 mL : 1 mL : 1 mL), LiOH (10 equiv.); (b) hydrogen chloride-1,4-dioxane; (3) cyclization: EDCI (1.2 equiv.), HOBt (1.5 equiv.), Et_3N (4.5 equiv.), DMF (60 mL) at 50 °C under air for 12 h. [b] Isolated yield after the last two steps.

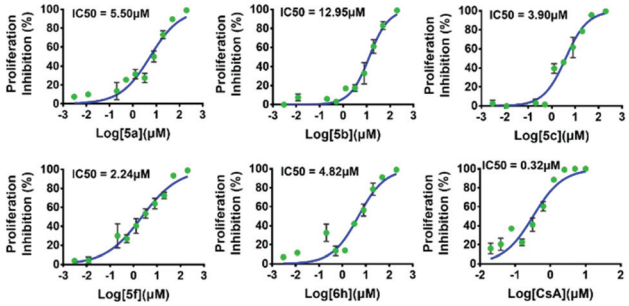


Fig. 2 Inhibitory effects of the indicated compounds on LPS-induced murine splenocyte proliferation.

macrolactams **5a–5h** were investigated in different biological assays. To our delight, compounds **5a**, **5c**, **5f** and **5h** exhibited low cytotoxicity and decent inhibitory activity on lipopolysaccharide (LPS)-induced B cell proliferation with IC_{50} values of 5.50, 3.90, 2.24 and 4.82 μM, respectively, while they hardly affected Con A-induced T cell proliferation (Table S1† and Fig. 2). In particular, **5c** and **5f** induced excellent suppression of B cell proliferation among the aforementioned compounds (Fig. S1†). It is acknowledged that the B cell receptor (BCR) and the Toll-like receptor (TLR) promote B cell responses in two distinct signaling pathways. We thus evaluated early activation and antibody secretion on purified murine $CD19^+$ B cells stimulated by TLR-ligand and anti-IgM/CD40 antibodies (Abs), respectively.

The results showed that both compounds **5c** and **5f** dramatically constrained the early activation status of B cells upon TLR4 ligand (TLR4-L, LPS) and BCR stimulation (Fig. S1†). Furthermore, compounds **5c** and **5f** could concentration-dependently impede IgG1, IgG2b, IgG3 and IgE secretion induced by TLR4-L. Besides, addition of compound **5c** decreased IgG1, IgG2b and IgM levels in the culture conditioned with anti-IgM/CD40 Abs, while compound **5f** only exerted a moderate impact on IgE production (Fig. 3).

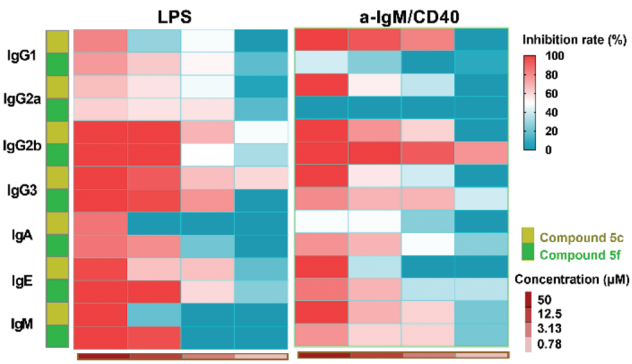


Fig. 3 Compounds **5c** and **5f** suppressed antibody production from LPS and anti-IgM/CD40-primed $CD19^+$ B cells. Primary murine $CD19^+$ B cells were cultured with LPS or anti-mouse IgM and purified hamster anti-mouse CD40 mAb in the absence or presence of the compounds (50, 12.5, 3.13, and 0.78 μM) in 96-well plates for 6 days to determine antibody production. The heat map shows the inhibitory rate of a particular class or isotype of immunoglobulins listed on the left side as IgG1, IgG2a, IgG2b, IgG3, IgA, IgE and IgM. Left panel: LPS-stimulated cultures; right panel: anti-IgM/CD40-stimulated cultures.

In summary, we have developed a highly chemoselective, native carboxylic acid directed Rh(III)-catalyzed C–H activation alkylation to directly introduce CF_3-substituted ketones. On the basis of this finding, we described a biomimetic B/C/P strategy that enables the efficient and rapid assembly of natural skeleton-derived building blocks, such as aspirin, chalcone, and amino acid (AA) analogs, to CF_3-bearing benzannulated macrolactams. Moreover, the representative compounds exhibited decent immunosuppressive effects on B cells *in vitro* and they could have potential application as novel immunosuppressants in autoimmune disease treatment.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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