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Methylation

Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation Reactions

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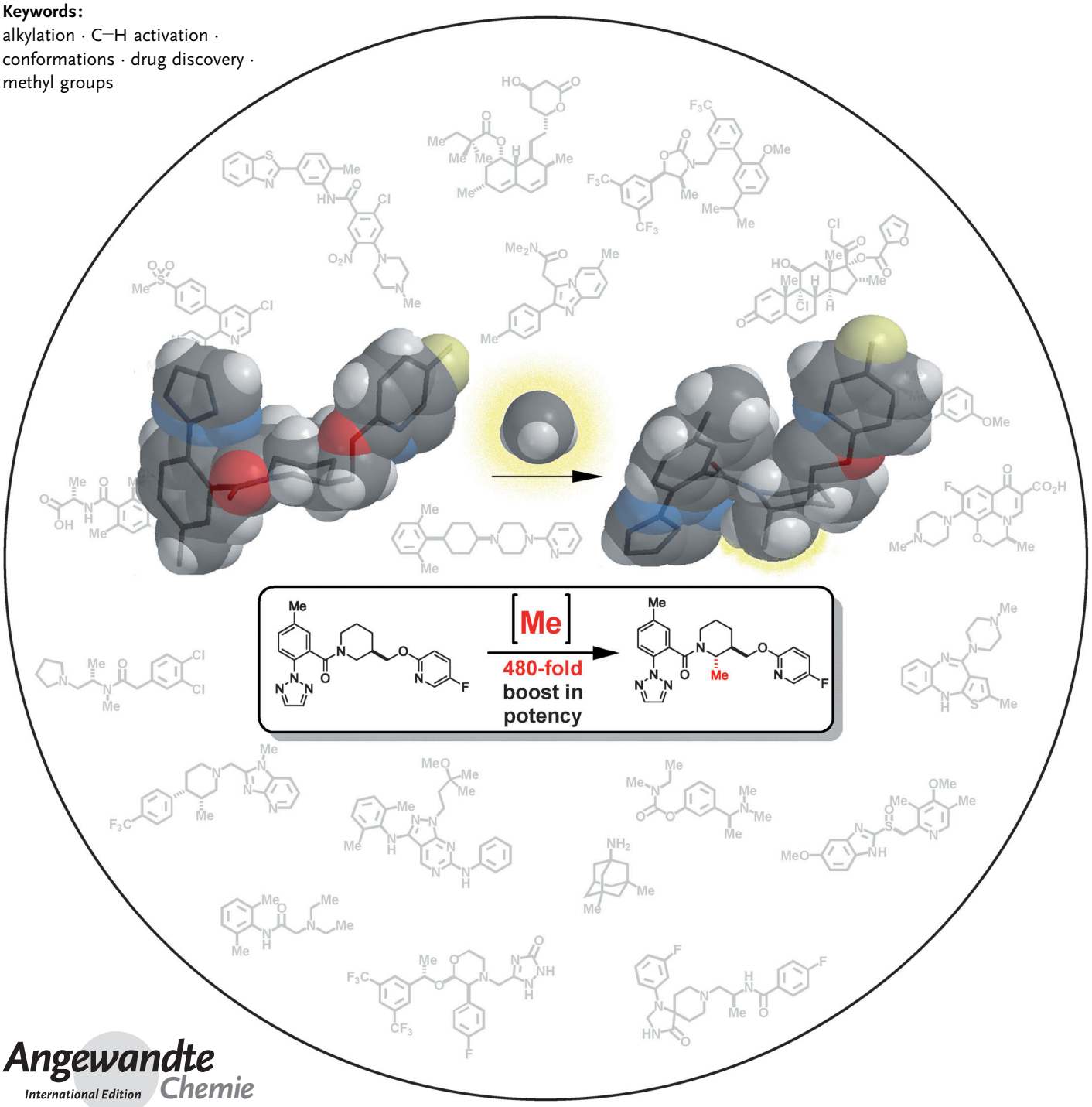

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The methyl group is one of the most commonly occurring carbon fragments in small-molecule drugs. This simplest alkyl fragment appears in more than 67% of the top-selling drugs of 2011 and can modulate both the biological and physical properties of a molecule. This Review focuses on so-called magic methyl effects on binding potency, where the seemingly mundane change of C–H to C–Me improves the IC_{50} value of a drug candidate more than 100-fold. This discussion is followed by a survey of recent advances in synthetic chemistry that allow the direct methylation of $C(sp^2)$–H and $C(sp^3)$–H bonds. It is our hope that the relevance of the meager methyl group to drug discovery as presented herein will inspire reports on new C–H methylation reactions.

From the Contents

1. Introduction

The methyl group is one of the most prevalent functionalities in biologically active molecules. A survey of Njardarson's Top 200 Drugs of 2011 shows that more than 67% of small-molecule drugs contain at least one methyl group bound to a carbon atom,[1,2] and a recent review highlights the importance of methyl groups in biologically active molecules.[3] A selection of methylated drugs is presented in Figure 1. During the exercise of designing a drug candidate, methyl groups are commonly installed in an effort to improve a molecule's biological activity and physical properties. Therefore, synthetic reactions that install methyl groups with ease are of value to the pharmaceutical industry.

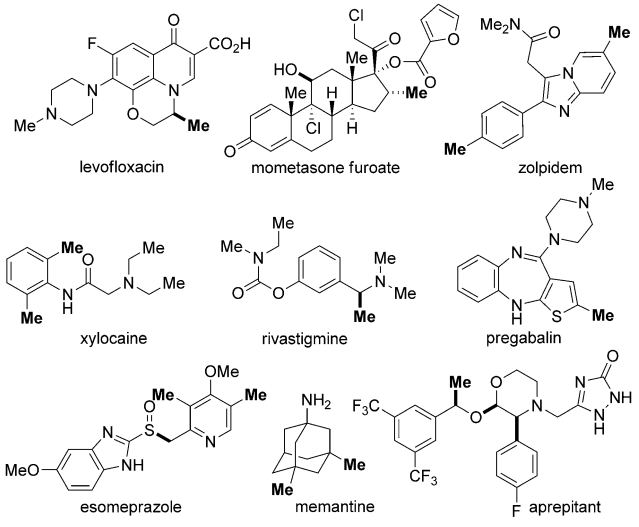

Figure 1. Small-molecule drugs containing a carbon-bound methyl group. Methyl groups that would be challenging to install without resorting to de novo synthesis are in bold.

Methylation is used to optimize many properties of a drug candidate (Figure 2a). For example, methylating next to a metabolic hot spot, as in simvastatin (**1**), might sterically block metabolism and lengthen the half-life ($t_{1/2}$).[4] Conversely, if a drug candidate is long-lived and excreted from the body at a rate too slow for the desired dosing regimen, for example one pill a day, a medicinal chemist may methylate to introduce a new metabolic hot spot and decrease the half-life, as was the case with etoricoxib (**2**).[5] Methylation can also have a favorable effect on solubility[6] or selectivity against off-targets (**3**).[7] Methylation can convert an agonist into an antagonist[8] or a partial antagonist into a negative allosteric modulator.[9] Indeed methylation can have a favorable effect on binding affinity, as in the case of the CETP inhibitor **4**.[10] There are several reasons why an increase in methylation might affect biological activity. Fundamentally, one can consider that 6 of the 20 natural amino acids bear a methyl group, so proteins have various patterns of methylation.[11] It thus stands to reason that molecules designed to interact with biological systems will benefit from having various patterns of complementary methylation.

2. The Magic Methyl Effect

The small improvements in binding affinity observed upon introducing a methyl group have been attributed to desolvation effects.[12] Increased methylation reduces the free energy of desolvation required to strip a ligand of solvated water molecules when it transfers from an aqueous environment to the greasy cavity of a protein (Figure 2b).[13] In this way, methylation can energetically favor binding and lower the IC_{50} value. Estimates place the value for $\Delta\Delta G_{transfer}$ upon a proton for methyl replacement at about 0.8 kcal mol^{-1} for transfer from water to a protein.[14] This corresponds to an approximate 3.5-fold boost in potency from methylation based on $\Delta\Delta G_{transfer}$ alone. A more empirical evaluation of literature examples by Jorgensen and co-workers suggested that a single methyl group might boost potency approximately 10-fold if the new methyl group sits nicely in a hydrophobic

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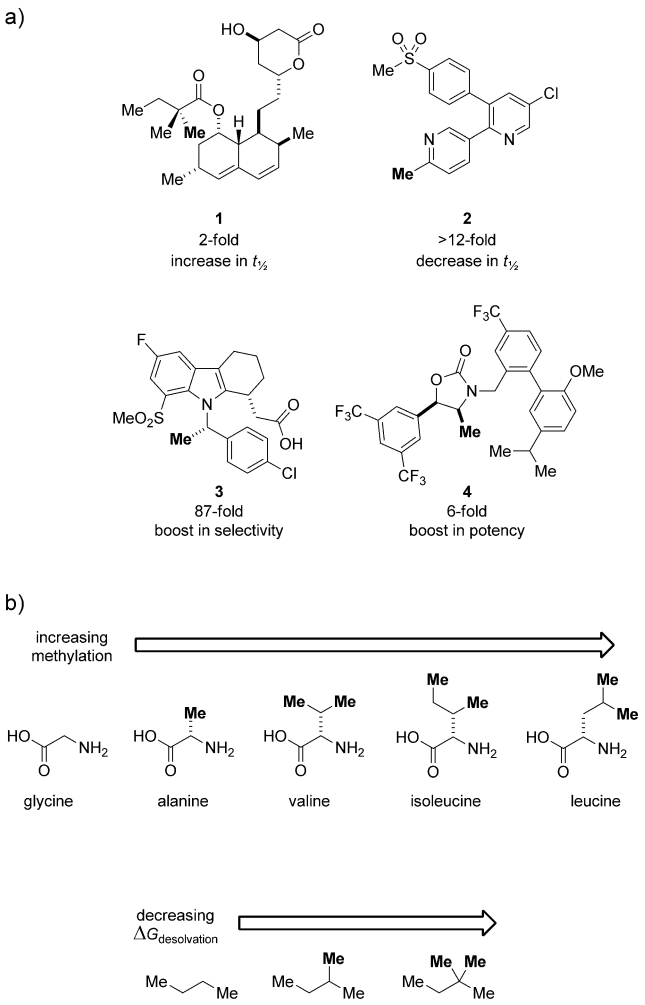


Figure 2. a) Methylation in the optimization of drug candidates: the effects listed refer to observations made by replacing a C–H with C–Me in the highlighted position. b) Methylated amino acids and the effects of methylation on the desolvation energy.

pocket of the active site.[15] In an extreme example, a 43-fold boost in potency upon methylation was attributed to a well-aligned hydrophobic interaction.[16]

It cannot be assumed, however, that installing a methyl group will always lead to an increase in potency. There must be space in the active site to accommodate the methyl group. In fact, a statistical analysis of more than 2100 recent examples from the medicinal chemistry literature showed that installation of a methyl group is just as likely to decrease affinity as it is to increase affinity.[15] Of those instances where introducing a methyl group leads to a more potent binder, there are rare cases where the increase in potency is profound: at times exceeding two orders of magnitude. Such increases in potency are far more than could be expected from the three- to tenfold potency boost based on desolvation effects, and are colloquially referred to as "magic methyl effects" in the medicinal chemistry community.[17] Four examples of the magic methyl effect are shown in Figure 3 where a simple C–H to C–Me replacement improved the IC_{50} value by as much as 590-fold per installed methyl group.[18–20] A compounding effect is observed with doubly methylated analogue **12**, where each newly installed methyl group leads to a surprising 1067-fold increase in potency.[21]

Magic methyl effects on binding affinity likely stem from an increase in shape complementarity between the unbound substrate and the active site of the protein in the bound state. In other words, the newly introduced methyl group gears the conformation of the ligand so that its three-dimensional shape more closely matches the conformation when bound in the active site, thus decreasing the conformational reordering required upon binding.[22] This is nicely illustrated by the examples of binding to the p38α MAP3 kinase (**5**/**6**) and orexin receptor (OX_1R) (**7**/**8**), where conformational information has been published (Scheme 1).

Compounds **5** and **6** were designed as inhibitors of p38α MAP3 kinase.[18] Methylation of **5** to give **6** resulted in a more than 208-fold boost in potency, so we deem this methylation to be magic. This example was studied computationally by Jorgensen and co-workers, who showed that a torsional twist induced by the *ortho*-methyl group leads to a low-energy conformation that more closely resembles the conformer observed in the X-ray crystal structure of the protein–inhibitor complex. The dihedral angle of the biaryl bond in **5** was calculated to be 50°, whereas installation of an *ortho*-methyl (**6**) twists this dihedral angle out to 65° (Scheme 1). When **5** or **6** binds to p38α MAP3 kinase, the dihedral angle of the biaryl bond is held at 85° (**13**). Thus **6** is 15° closer to the conformation it will assume in the active site than is **5**. Moreover, the torsional twist induced in **6** will be

Tim Cernak was born in Montreal, Canada, in 1980. He completed a BSc at UBC Okanagan before returning to Montreal in 2002 to pursue PhD studies on the total synthesis of palau'amine with James Gleason at McGill University. In 2007 he began postdoctoral studies with Tristan Lambert at Columbia University. These studies involved the development of catalytic heterocyclization reactions. Since 2009, he has been a member of the Medicinal Chemistry team at Merck & Co., Rahway, NJ. His research interests include medicinal chemistry, catalysis, and C–H activation.

Heike Schönherr studied chemistry at the Technical University of Chemnitz and University of Leipzig. She completed her PhD in 2010 with Prof. Dr. Christoph Schneider in the field of natural product synthesis, and then started postdoctoral work as a DFG Fellow with Prof. Dr. James Leighton at Columbia University on enantioselective iso-Pictet-Spengler reactions. Currently she is a researcher at Columbia University Medical Center in the Department of Ophthalmology, where together with Prof. Dr. Janet Sparrow she is investigating age-related macular degeneration. In late 2013, Heike will join the Medicinal Chemistry team at AstraZeneca in Waltham, MA.

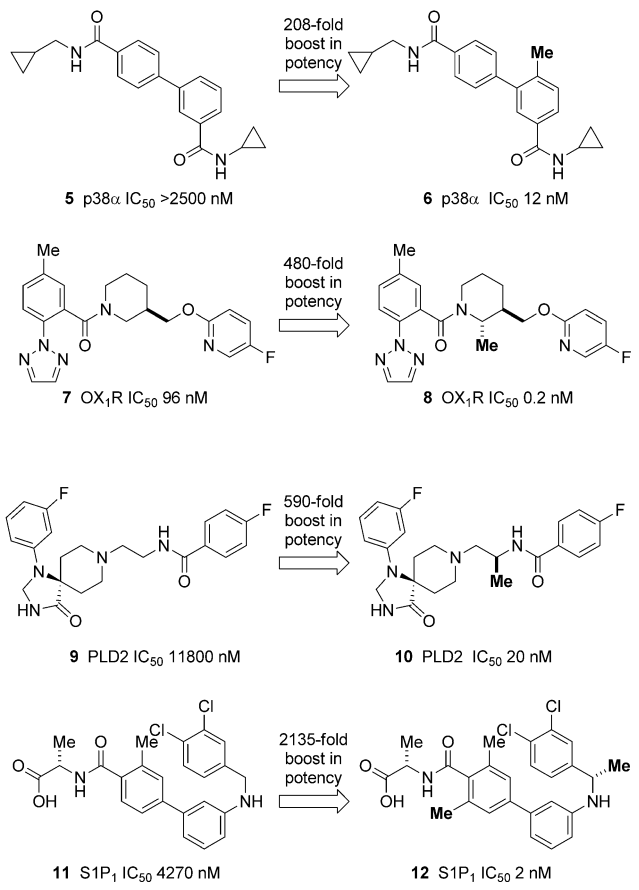
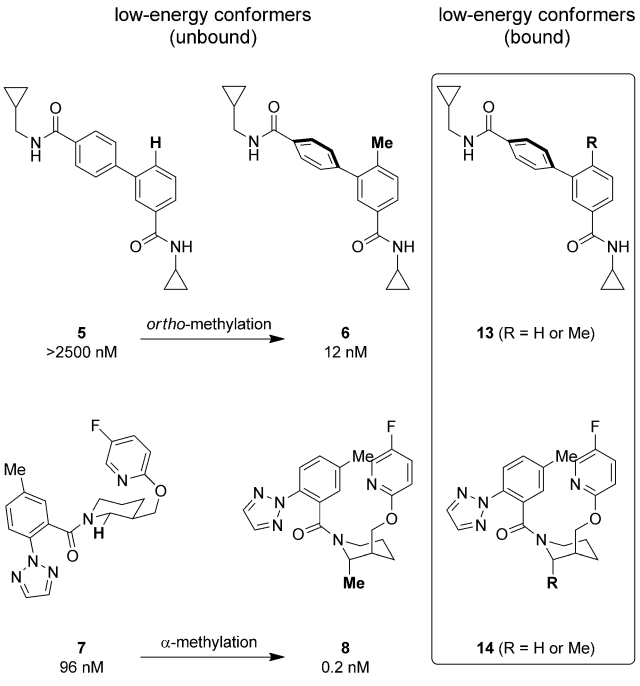


Figure 3. Examples of C–H methylation where a magic methyl effect was observed.



Scheme 1. Conformational preorganization is a possible cause of the magic methyl effect.

locked, since the barrier to atropisomerization is high for **6** compared to **5**. Therefore, the methyl group gears **6** so that it looks more like its protein-bound conformer and there is a surprisingly beneficial effect on binding affinity.

The 480-fold boost in potency observed for compounds **7** and **8** is also believed to be from the induction of a profound conformational change leading to a low-energy conformer that more closely approximates the bound conformation. These compounds are dual antagonists of the orexin-1 and orexin-2 receptors under development at Merck for the treatment of insomnia. Crystallographic data on the bioactive conformer is unavailable in this example, but empirical evidence suggests that the bound conformation of a dual orexin receptor antagonist (DORA) is U-shaped, as in **14**.[23] Based on the hypothesis that a DORA should be U-shaped, **8** was designed with the intent of enforcing an axial arrangement of the 3-methyleneoxy substituent by installing a methyl group in the position α to the amine. NMR studies on **8** confirmed that the molecule exists in a U-shaped diaxial conformation with the amide twisting to minimize the 1,3-diaxial interaction between the methyl group and the two aryl moieties held closely together presumably by π stacking. The diaxial arrangement was also observed in an X-ray crystal structure of **8** (unbound). An analogue where the α-methyl group was *cis* to the 3-methyleneoxy group was 100-fold less active than **8**: presumably the U-shaped conformation apparently required for biological activity was not attained when the alkyl groups are *cis*, since one substituent will be equatorial.

Conformational biases can be introduced with many groups other than methyl. For example, the virtuous fluoro substituent may impart a conformational change through stereoelectronic effects, but fluoro may be unstable if installed in the position α to heteroatoms, as in **14** (R = F). In contrast, the trifluoromethyl group is bulky enough to sterically induce a conformational lock and is stable when introduced next to heteroatoms. However, one runs the risk of violating Lipinski's rules[24] when installing a lipophilic trifluoromethyl group ($\Delta MW = 68\ \mathrm{g\,mol^{-1}}$, $\Delta c\log P \approx 0.9$) if the molecular weight and log*P* value of the starting lead compound is already high. The advantage of the methyl group is that its installation makes only a small change to the physical properties of a molecule ($\Delta MW = 14\ \mathrm{g\,mol^{-1}}$, $\Delta c\log P \approx 0.5$). Large greasy molecules have a poor track record of becoming drugs, therefore, it is the job of the medicinal chemist to optimize drug leads by adding as few superfluous atoms as possible.[25] Progress in these endeavors can be measured by tracking parameters such as lipophilic ligand efficiency (LLE).[26] In the extreme example of the PLD2 inhibitor **10**, the new methyl group adds very little grease ($\Delta c\log P = 0.36$),[27] yet improves potency from 11800 nM to 20 nM. This corresponds to a staggering improvement of 3.1 log units in the LLE. In terms of value, a methyl group that leads to a profound improvement in potency is hard to beat.

Figure 4 summarizes some guiding principles for the strategic introduction of methyl groups when searching for magic methyl effects. As noted by Jorgensen and co-workers, the most profound effects tend to occur when the new methyl group induces a significant change in conformation. We have

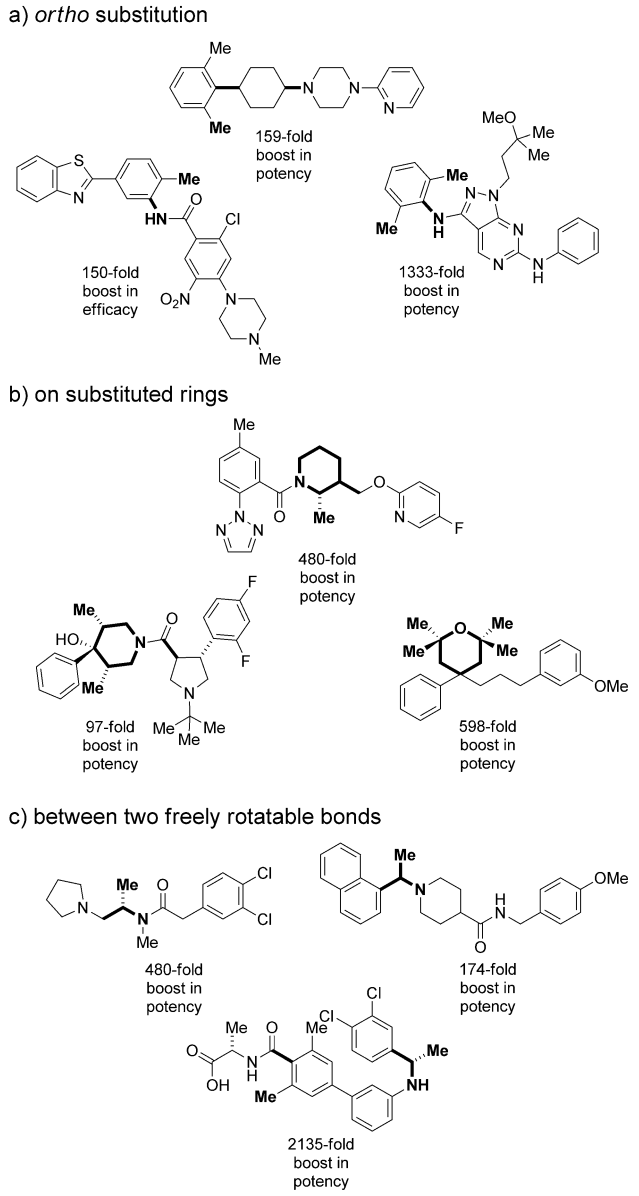


Figure 4. Guiding principles for the strategic introduction of methyl groups when probing for a magic methyl effect. Methyl groups drawn in bold are responsible for the observed boost in potency.

seen a trend that the most significant boosts in potency occur when the new methyl group is installed in one of the following positions:

a) *ortho* to a large rotatable substituent on an aryl ring;[28–30]

b) on substituted rings where an axial or equatorial preference of substituents can be influenced;[19,31,32]

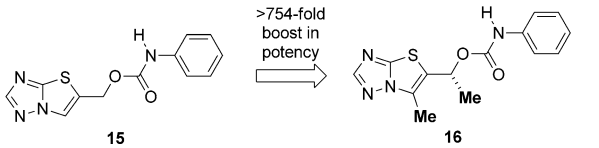
c) between two freely rotatable bonds that are substituted with bulky groups.[21,33,34]

Our list is not expected to be all-inclusive, but serves as a starting point to guide methylation studies when increases in potency are desired. Interestingly, a combination of arrangements (a) and (c) contributes to the 2135-fold potency enhancement observed with **12**. With a few exceptions,[35] we observed that methylating at sites where little conformational bias is expected led to an approximate 10-fold improvement in potency at best. We attribute these smaller gains to hydrophobic and desolvation effects. Presumably, the biggest gains in potency will be realized when the interplay of conformational, hydrophobic, desolvation, and other effects are cooperatively aligned.[36]

It must be emphasized that the likelihood of discovering a >100-fold boost in potency by installing a single methyl group is extremely low. However, if synthetic chemistry allows facile access to a methylated analogue of a drug lead then the potential payoff in the lipophilic ligand efficiency merits such explorations.

We have highlighted examples of magic methyl effects in terms of binding potency, but as shown in Figure 2 a methylation can have other biological effects. Profound effects can be observed when the newly installed methyl group induces a dramatic conformational change, as in **6** and **8**. Even though profound methyl effects occur only rarely, small beneficial effects on biological activity are sometimes observed on exchanging C–H for C–Me; therefore methylation is a common strategy employed by the medicinal chemist for optimizing drug leads. An excellent example of a medicinal chemistry methylation strategy was reported by a team at GlaxoSmithKline during the optimization of mGluR5 antagonist **16** (Figure 5).[37] Various patterns of methylation were explored on the thiazole ring, the benzylic carbon, and the carbamate nitrogen atom of a high-throughput screening hit. By "walking" methyl groups around the periphery of **15** the team was able to locate a 40 nM inhibitor with a methyl group on the thiazole and a chiral methyl group at the benzylic position.

In terms of synthesis, there has been great success in recent years in the development of methods for the installation of trifluoromethyl groups.[38] Very recently difluoromethyl and fluoromethyl groups[39] have also enjoyed the attention of the synthetic community. Although synthetic methods to install the simple methyl group have a much



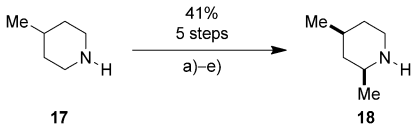
	R^1	R^2	R^3	R^2 stereochemistry	mGluR5 IC_{50} (nM)
	H	H	H	---	>30000
	H	Me	H	racemic	~10000
	Me	H	H	---	>30000
	Me	Me	Me	racemic	>30000
	Me	Me	H	*S*	>10000
	Me	**Me**	**H**	***R***	**40**

Figure 5. Optimization of mGluR5 antagonist **16** by methylation.

longer history, C–H methylation presents a significant challenge in many contexts. For example, all of the analogues described by the GlaxoSmithKline team in Figure 5 were prepared by de novo synthesis, thus highlighting the need for new methods for direct methylation. Advances in the direct installation of the smallest alkyl group are covered in the next section.

3. Recent Advances in C–H Methylation

Given the potential benefits methyl groups bring, magic or otherwise, it is common that a medicinal chemist will synthesize and examine methylated variants of a drug lead. A methyl group is small (15 g mol^{-1}, ca. 30 Å^2) and there is only a small lipophilic penalty to pay for its installation ($\Delta\log P \approx 0.5$). Thus, in the fine-tuning stages of lead optimization the medicinal chemist will benefit from the ability to quickly methylate a lead molecule. Currently, the replacement of C–H by C–Me can sometimes be achieved on an advanced drug lead if the C–H moiety is acidic, as in methylation at the α position to a carbonyl group via the enolate. There are also several synthetic options for methylating heteroatoms (e.g. OH→OMe), such as treatment with methyl iodide or diazomethane. But how would one install one of the highlighted methyl groups in the drugs presented in Figure 1? Currently, few reactions exist that enable such transformations to be achieved in a single step. A recent example from an otherwise concise total synthesis of cermizine C highlights the difficulty in achieving a C–H to C–Me conversion. In this case, methylation at the 2-position of a piperidine (**17**) required five synthetic steps (Scheme 2).[40] In many instances methylation of an advanced intermediate can only be achieved by de novo synthesis. Given the tight timelines of medicinal chemistry endeavors, it can be difficult to justify embarking on a multistep methylation of a drug candidate where the payoff is unknown. However, the potential reward of discovering a magic methyl effect merits exploration of methylated chemical space. Therefore, innovative reactions that facilitate currently challenging C–H methylation transformations such as the one presented in Scheme 2 are needed.

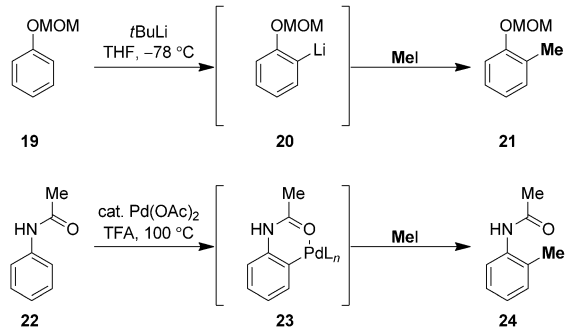


17 18

Scheme 2. C–H methylation of **17** by multistep synthesis. Reagents and conditions: a) Boc_2O, THF/H_2O, NaOH; b) 20 mol% $RuO_2 \cdot x H_2O$, $NaIO_4$, EtOAc/H_2O; c) MeMgBr; d) TFA then NaOH; e) $Pd(OH)_2/C$, H_2 (45 psi). Boc = *tert*-butoxycarbonyl, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

3.1. Methylation of C(sp^2)–H Bonds

Recent advances in C–H activation now address some of the direct C–H methylation disconnections, and we survey these advances in the remainder of this Review. The most common methods for the direct conversion of a C–H bond into a C–Me bond are 1) the deprotonation of an acidic C–H bond by a strong base followed by quenching of the intermediate anion **20** with an electrophile such as methyl iodide or dimethylsulfate;[41] and 2) the insertion of a metal into a C–H bond (**23**) followed by interception of the organometallic intermediate with a nucleophilic or electrophilic methyl source (Scheme 3).[42] For the C–H methylation



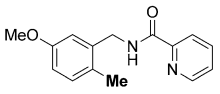
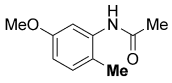
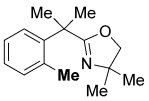
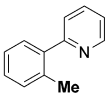
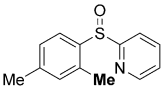
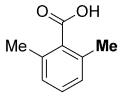
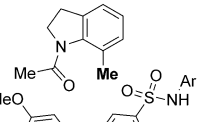
Scheme 3. Directed methylation of C(sp^2)–H bonds by directed *ortho*-metalation or palladium(II)-catalyzed C–H insertion. MOM = methoxymethyl.

of C(aryl)–H bonds, one could consider a directed *ortho*-metalation procedure. This method is well developed and allows *ortho*-methylation as long as the substrate tolerates strongly basic conditions. Several reviews on the directed *ortho*-metalation of aryl groups are available and the reader is referred to these for details.[43] In 1984 Tremont and Rahman reported a Pd-mediated directed C–H alkylation of acetanilides with alkyl halides including methyl iodide.[44] This transformation nicely complements the directed *ortho*-metalation procedure because it occurs under acidic conditions. In one example, catalysis with 10 mol% $Pd(OAc)_2$ was demonstrated by employing AgOAc as a stoichiometric oxidant. This report on directed C–H alkylation demonstrated the feasibility of using weakly coordinating directing groups for catalytic C–H methylation.

In recent years there has been considerable application of the palladium-catalyzed alkylation reported by Tremont and Rahman. In just one of these cases was C–H methylation the end goal of reaction development as opposed to a single entry in a broader study on C–H alkylation. Examples of directed C–H methylation are shown in Table 1.

A variety of methyl sources including methyl iodide (entries 1 and 2), tetramethyltin (entry 3),[45] dicumyl peroxide (entry 4),[46] and methylboronic acid (entries 5 and 6)[47,48] have been applied successfully in reactions catalyzed by palladium(II) acetate, which is by far the most popular catalyst for directed C–H methylations. Some key advancements in directed C–H methylation with methyl iodide include a recent report from the Chen research group that details the use of O_2 as the sole oxidant (entry 1),[49] while Jang and Youn report conditions that allow the reaction to proceed in a reasonable amount of time at room temperature (entry 2).[50] Sanford and co-workers have recently developed a mild procedure that makes use of methyl trifluoroborate

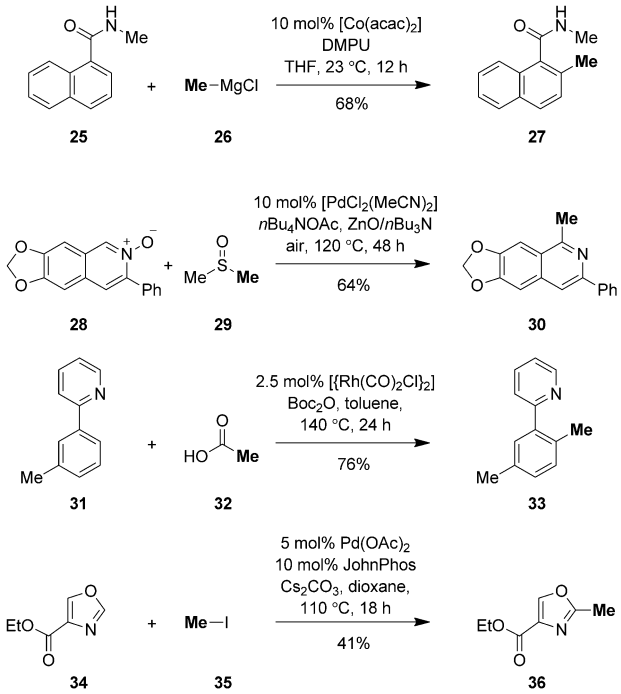
Table 1: Directed methylation of C(sp^2)–H bonds catalyzed by $Pd(OAc)_2$.

Entry	Methyl source	Conditions	Product	Yield
1	**Me**I	5 mol% $Pd(OAc)_2$ O_2, NaOTf, K_2CO_3 *t*AmOH, 125 °C, 36 h		90%
2	**Me**I	5 mol% $Pd(OAc)_2$ AgOAc, $Cu(OTf)_2$ TFA, CH_2Cl_2, 25 °C, 11 h		86%
3	$Sn\mathbf{Me}_4$	10 mol% $Pd(OAc)_2$ BQ, $Cu(OAc)_2$ MeCN, 100 °C, 40 h		86%
4	$(Ph\mathbf{Me}_2CO)_2$	10 mol% $Pd(OAc)_2$ neat, 140 °C, 12 h		54%
5	**Me**$B(OH)_2$	10 mol% $Pd(OAc)_2$ air, BQ, AgOAc *t*AmOH, 100 °C, 20 h		62%
6	**Me**$B(OH)_2$	10 mol% $Pd(OAc)_2$ BQ, Ag_2CO_3 *t*BuOH, 100 °C, 3 h		75%
7	**Me**BF_3K	10 mol% $Pd(OAc)_2$ MnF_3, AcOH, TFE/H_2O, 40 °C, 3 h,		83%
8	**Me**$B(OH)_2$	20 mol% $Pd(OAc)_2$ BQ, K_2HPO_4, Ag_2CO_3, *t*AmOH, 110 °C, 24 h, Ar = C_6F_5		71%

with a manganese promoter (entry 7).[51] In a nice application of this method to real-world substrates, Yu and co-workers in collaboration with Pfizer demonstrated a late-stage methylation on an analogue of the anti-inflammatory drug celecoxib (entry 8).[52]

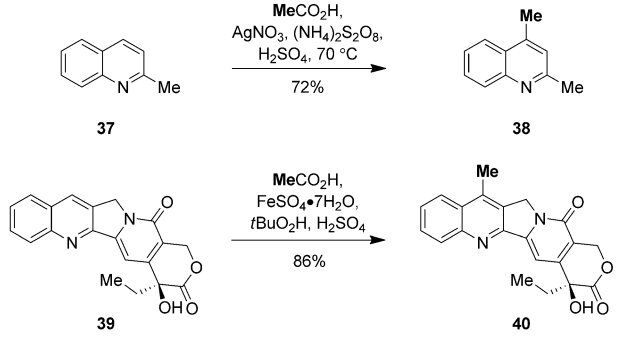
Catalysts other than $Pd(OAc)_2$ allow the application of other methyl sources (Scheme 4). For example, methylmagnesium chloride (**26**) proved suitable in the presence of a catalytic amount of cobalt(II) acetoacetate.[53] A peculiar transformation using DMSO (**29**) as the methyl source was accomplished with palladium(II) chloride bis(acetonitrile). In this case, the *N*-oxide substrate **28** likely serves as the oxidant.[54] Recently, a rhodium system was described that allowed the use of acetic acid **32** as a methyl source.[55] A direct methylation of oxazole **34** catalyzed by Pd·JohnPhos has also been developed.[56]

All of the C–H methylation procedures presented so far detail directed reactions where some proximal group guides the methyl group to the site of reaction. A complementary approach would be to access the innately reactive C–H bonds[57] and, to our knowledge, the only method to methylate such bonds are the additions of methyl radical to heterocycles



Scheme 4. Directed methylation of C(sp^2)–H bonds with other catalysts. acac = acetylacetonoate, DMPU = *N*,*N*′-dimethylpropylurea.

first reported by Minisci (Scheme 5).[58] In 1971, it was demonstrated that the methyl radical generated from acetic acid by a silver salt and an oxidant adds into protonated heterocycles such as 2-methylisoquinoline (**37**).[59] Subsequently, a related methylation of camptothecin (**39**) by using ferrous sulfate and *tert*-butylhydroperoxide was achieved in good yield.[60]

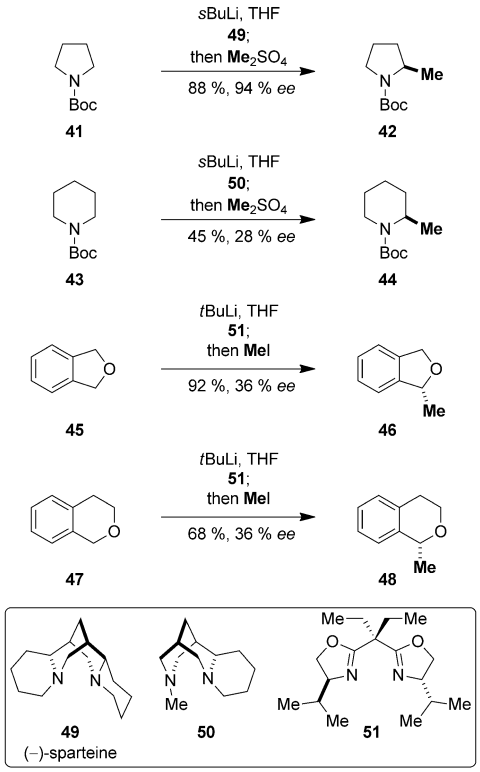


Scheme 5. Addition of a methyl radical to heteroaromatic substrates.

3.2. Methylation of C(sp^3)–H Bonds

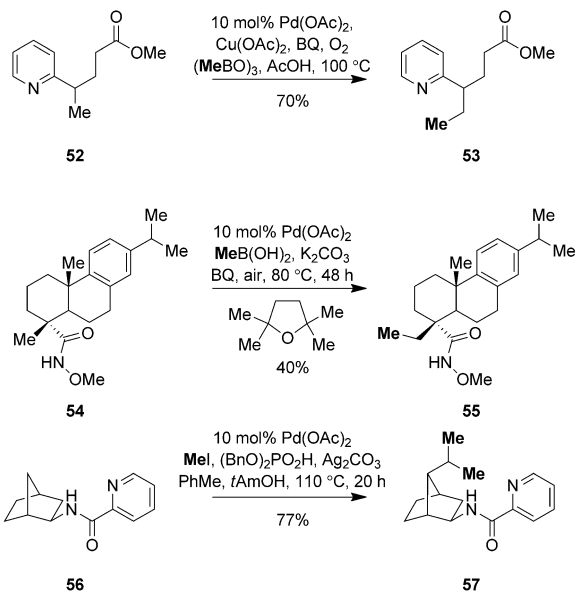
The C–H methylation at an sp^3-hybridized carbon atom has been considerably less investigated. As with the C–H methylation of sp^2 carbon centers, there are two general approaches: 1) deprotonation with a strong base followed by quenching with a methyl electrophile in analogy to the directed *ortho*-metalation of aryl groups; and 2) directed C–H methylation in the presence of palladium(II) acetate.

Beak et al. first showed that *N*-Boc-pyrrolidines such as **41** were viable substrates for α-deprotonation followed by quenching with an electrophile.[61] Importantly, the inclusion of a chiral amine such as (−)-sparteine (**49**) renders the reaction enantioselective with up to 94% *ee*. More recently, a team at Merck has extended this reaction to piperidines such as **43**, with **50** as the preferred ligand.[62] Enantioselectivities are low for the direct quenching of the lithium anion with methyl iodide, but a two-step procedure where the lithium anion is first converted into an organotin intermediate that is then methylated with dimethyl sulfate improved the *ee* value to 74% and 44% overall yield. A related transformation was applied to ethers, with the substrate scope limited to isoflavins such as **45** and isochromans such as **47**.[63] In these cases, ligand **51** outperformed the chiral amine bases, but enantioselectivities remain low (Scheme 6).



Scheme 6. Methylation of C(sp^3)–H bonds with a strong chiral base.

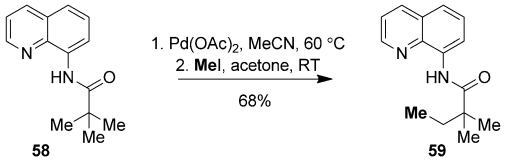
Only recently have directed C–H methylations of sp^3-hybridized carbon atoms been demonstrated (Scheme 7). In a first example, Yu and co-workers demonstrated that a variety of heterocycles (e.g. **52**) competently directed palladium(II) acetate to an adjacent alkyl group and allowed reaction with trimethylboroxine or methylboronic acid.[64] In some cases dimethylation was observed as a minor product, thus indicating that methylation is possible on secondary sp^3-hybridized carbon atoms, albeit at a slower rate. As an extension of this study, hydroxamic esters such as **54** were shown to be capable directing groups, and the copper(II) cooxidant was unnecessary in this case.[65] Most recently, the Chen and co-workers reported an impressive procedure for



Scheme 7. Directed methylation of C(sp^3)–H bonds catalyzed by Pd(OAc)$_2$. BQ = benzoquinone, *t*Am = *tert*-amyl.

building up branched alkyl groups on sp^3-hybridized carbon atoms one carbon at a time, such as the isopropyl group in **57**, by treating picolinamides with an excess of methyl iodide.[66]

Shabashov and Daugulis have described a palladium(II) acetate coupling of C(sp^3)–H bonds with alkyl iodides (Scheme 8).[67] A variety of alkyl iodides performed well



Scheme 8. Directed methylation of C(sp^3)–H bonds promoted by Pd(OAc)$_2$.

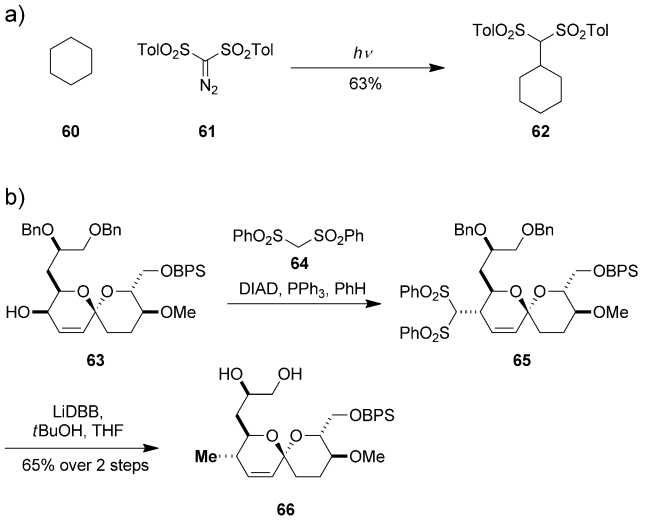
under catalytic conditions, but methyl iodide was only demonstrated as a viable reaction partner in a mechanistic study carried out with the presence of a stoichiometric amount of palladium (**58** to **59**). Methyl iodide would most likely be a compatible reaction partner in the catalytic process.

3.3. New Methylation Reagents

Most of the examples we have highlighted are guided C–H methylations in that the reaction occurs proximal to some directing group. The development of innate C–H methylation procedures that target either the weakest (electronics) or most accessible (sterics) C–H bond will be a valuable complementary development. For example, a C–H insertion with diazomethane analogous to the available carbene insertion reactions would be a powerful method of

C–H methylation.[68] To our knowledge, a C–H insertion with diazomethane has not been reported, although a theoretical treatment was described.[69] While the common surrogate trimethylsilyldiazomethane has not to our knowledge been used in C–H insertion reactions, it has been shown to cyclopropanate alkenes under Rh-catalyzed conditions[70] and to insert into Pd–C bonds in cascade reactions.[71]

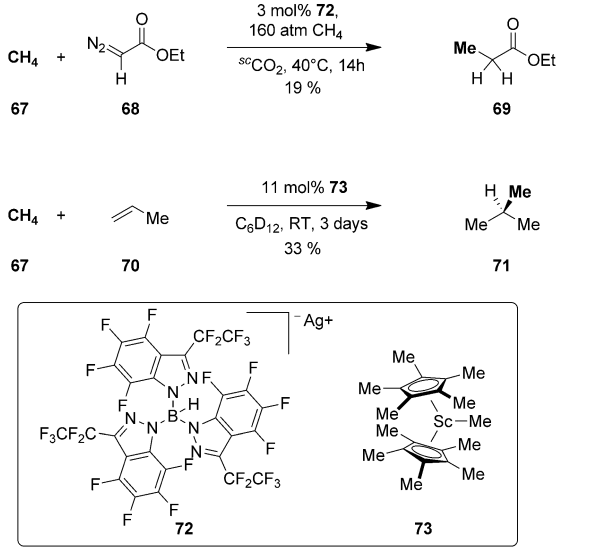
The less common methyl surrogate bis(toluenesulfonyl)-diazomethane (**61**) was shown to productively insert into cyclohexane **60**, albeit when the latter was employed as the solvent (Scheme 9a).[72] This study focused on the photo-



Scheme 9. a) C–H insertion with bis(tolyl)diazomethane and b) the use of bis(aryl)sulfonamides as methyl surrogates. Bn = benzyl, BPS = biphenyl(*tert*-butyl)silyl, DIAD = diisopropyl azodicarboxylate.

decomposition of bis(toluenesulfonyl)diazomethane and not on C–H methylation, so the reduction of **62** to methylcyclohexane was not demonstrated; However, multiple reports detail the reduction of bis(arenesulfonyl)methanes to methyl groups.[73] In one elegant example towards a total synthesis of spirastrellolides A and B by Smith et al., bis(benzenesulfonyl)methane (**64**) was employed as a nucleophile in a Mitsunobu displacement and the product was reduced with LiDBB to achieve the conversion of an allyl alcohol into an allylmethyl group in two steps and 65% overall yield (Scheme 9b).[74]

The most atom economical way to install a methyl group would be from methane. A recent review of methane activation highlights the potential of natural gas (**67**) as a methylating reagent in the presence of transition-metal complexes as catalysts.[75] In one example, Perez and co-workers report the insertion of ethyl diazoacetate (**68**) into a methane C–H bond catalyzed by silver(I) complex **72** in a medium of supercritical carbon dioxide.[76] Likewise, Sadow and Tilley demonstrated the hydromethylation of propylene (**70**) with methane in the presence of scandium(III) catalyst **73** (Scheme 10).[77] Although these examples describe C–H activation of the reagent rather than the substrate, they



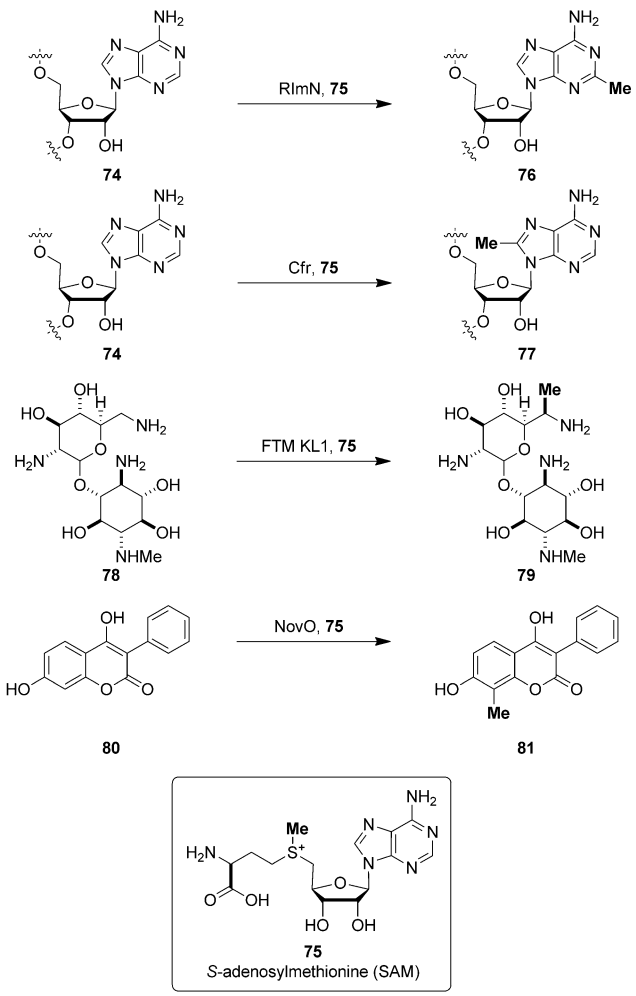
Scheme 10. Methane gas as a reagent for the methylation of small organic molecules. $^{sc}CO_2$ = supercritical CO_2.

serve to highlight an important future direction in the development of methylation reactions. As methane activation advances towards mild reaction conditions and broad functional group tolerance there will be exciting opportunities for synthetic methylation strategies on biologically relevant molecules.

3.4. Biocatalytic C–H Methylation

Methylation is among the most prevalent chemical modifications in biological systems and, thus, nature has devised powerful tools to install methyl groups. The topic of biocatalytic methylation has been reviewed recently,[78] and some impressive examples of well-studied biochemical methylations are presented in Scheme 11. RimN and Cfr are two enzymes that accomplish divergent methylations on an rRNA adenosine at C2 and C8, respectively.[79] Mechanistic and crystallographic studies[80] suggest that both reactions likely occur through a radical cascade mechanism. This subtle control of selectivity highlights the potential that biocatalytic methylations may one day offer. In an equally inspiring example, a late-stage C(sp^3)–H methylation catalyzed by fortimicin KL1 methyltransferase (FTM KL1) completes the synthesis of the secondary metabolite fortimicin KK1.[81]

S-Adenosylmethionine (**75**, SAM) is the most prevalent natural source of methyl groups and is the operative cofactor in all four examples in Scheme 11. At present, the utilization of SAM (**75**) is prohibited because of the cost, and systems to effectively recycle SAM have not yet been developed, thus limiting the scale of biocatalytic C–H methylations. To our knowledge, the largest in vitro C–H methylation so far accomplished was on a 30 mg scale during the conversion of **80** into **81** by the enzyme NovO.[82] As technical difficulties related to the use of SAM are overcome, the evolution of methyltransferases into viable reagents for small-molecule



Scheme 11. Application of methyl transferase enzymes for the late-stage methylation by using SAM (**75**) as the methyl source.

C–H methylation will be an important future direction in synthetic biology.

4. Conclusions

In comparison to its importance to the pharmaceutical industry, the methyl group is, in our opinion, underrepresented in recent synthetic chemistry. In contrast, the CF_3 group has received much attention from the synthetic community in the past decade. While the trifluoromethyl group is extremely important to the pharmaceutical industry and until recently its synthesis was extremely challenging, less than 5% of the top-selling drugs of 2011 have a CF_3 group, whereas more than 67% of these drugs contain a methyl group bound to a carbon atom. One reason the methyl group is so popular in drug discovery is the magic methyl effect: a rare but welcome phenomenon where installation of a methyl group induces a conformational change that can induce up to 590-fold boosts in potency. The pharmaceutical industry will benefit from new C–H methylation reactions and, therefore, the pioneering advancements in C–H methylation science presented herein should greatly facilitate the discovery of magic methyl effects by medicinal chemists.

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