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Late-stage oxidative C(sp³)–H methylation

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Summary Paragraph:

Frequently referred to as the “magic methyl effect”, installation of methyl groups, especially α to heteroatoms, has been shown to drastically increase the potency of bioactive molecules[1–3]. Current methylation methods display limited scope and have not been demonstrated in complex settings[1]. Herein we report a regio- and chemoselective oxidative C(sp^3)–H methylation method compatible with late-stage functionalization. A key to affecting this new chemistry was the combination of a highly site- and chemoselective C–H hydroxylation with a mild, functional group tolerant methylation. Using a small molecule manganese catalyst Mn(CF_3PDP) at low loading (substrate/catalyst = 200) afforded targeted C–H hydroxylation on heterocyclic cores while preserving electron neutral and rich aryls. Fluorine or Lewis acid assisted formation of reactive iminium or oxonium intermediates enabled the use of a modestly nucleophilic organoaluminum methylating reagent that preserves other electrophilic functionalities on the substrate. The late-stage C(sp^3)–H methylation is demonstrated on forty-one substrates housing sixteen different medicinally important cores incorporating electron-rich aryls, heterocycles, carbonyls, and amines. Eighteen pharmacologically relevant molecules with competing sites, including drugs (for example tedizolid) and natural products, are methylated site-selectively at the most electron rich, least sterically hindered position. Syntheses of two magic methyl substrates, an RORc inverse agonist and an $S1P_1$ antagonist, are demonstrated for the first time via late-stage methylation from the drug or its advanced precursor. Additionally, an unprecedented remote methylation of the B-ring carbocycle of an abiraterone analog is shown. The ability to methylate such complex molecules at late stages will reduce synthetic effort and thereby expedite broader exploration of the magic methyl effect in pursuit of novel small molecule therapeutics and chemical probes.

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Data availability The data that support the findings of this study are available in the Supplementary Information and from the corresponding author upon reasonable request.

Competing interests The University of Illinois has filed a patent application on the Mn(CF_3-PDP) catalyst.

Supplementary information is available in the online version of the paper.

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The introduction of methyl groups has the potential to drastically improve the biological activities of a drug candidate by altering its binding affinity, solubility, and metabolism[1–8]. Such changes have been demonstrated to increase the potency of lead compounds up to more than 2000 folds and to enable interrogation of biological processes (Fig. 1a)[6–8]. Although methyl groups are ubiquitous in small-molecule drugs[1], no general method is available to incorporate them in complex molecules at late stages. Accordingly, *de novo* synthesis, a rate-limiting step in drug discovery that impairs its overall atom-economy, is required[9,10]. A practical synthetic method that allows selective installation of methyl groups from C–H bonds at sites adjacent to heteroatoms, where the magic methyl effect is often most significant, would streamline diversification of drug leads and encourage more comprehensive investigations of this effect. Over the past decade, considerable progress has been made in developing C(sp^3)–H alkylation methods where the *N*-or *O*-heterocycle acts as a nucleophilic coupling partner[11–17]. Such cross-couplings have shown broad scope with respect to alkyl electrophiles but limited scope of the metalated heterocyclic intermediates generated via substrate-controlled deprotonation or single-electron transfer (SET). Cases demonstrated with methyl electrophiles have focused on simple azacycles [11,13,15–17]. Expanding the heterocyclic scope to include dissymmetric substrates, epimerizable stereocenters, electrophilic functionalities (e.g., carbonyl, nitrile), remote basic amines, heteroaromatics, and halogenated aromatics remains a major challenge to be overcome for widespread use in late-stage diversification. Additionally, while direct C–C bond forming reactions may be desirable for installing larger and/or functionalized alkyl groups, direct methylation often results in inseparable mixtures with the starting material due to the methyl group's small size and electron neutrality.

We sought to approach C(sp^3)–H methylation in *N*- and *O*-containing heterocycles in an oxidative fashion through a hydroxylated intermediate, with subsequent iminium or oxonium ion formation and methylation (Fig. 1b). Catalyst control could be leveraged to influence the site- and chemoselectivity of C–H hydroxylation in a broad range of heterocycles (Fig. 1c,d). Reports of alkylations of *N*-acyliminium ions are of limited scope[18–20]. Although C(sp^3–H oxidation α to heteroatoms has been well-demonstrated, substrate-controlled selectivities can afford poor site- and chemoselectivity thereby limiting examples in complex settings. Additionally, the strong hyperconjugative activation of hemiaminals and hemiacetals typically promotes overoxidation to the corresponding carbonyl, calling for reduction prior to or after methylation (Fig. 1b)[21–26].

The $Mn(CF_3PDP)(MeCN)_2(SbF_6)_2$ **1** catalyst was reported to uniquely control site- and chemoselectivity in hydroxylating strong methylene C(sp^3)–H bonds while tolerating halogenated arenes, although the tolerance for electron neutral or rich aromatic and some heteroaromatic rings remained a challenge (Fig. 1b)[27]. We questioned if sterically hindered catalyst **1** could result in faster C–H hydroxylation than alcohol oxidation for hyperconjugatively activated C–H bonds, and whether under milder oxidation conditions such a rate difference would increase chemoselectivity and yield for the hydroxylated product. Under the previously reported forcing conditions (10 mol% **1**, 5 equiv. H_2O_2)[27], oxidation of arylated γ-lactam **2** afforded a significant amount of over-oxidation to the corresponding imide (Fig. 2a, **4b**, 41%). Lowering the catalyst and hydrogen peroxide

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loadings (0.5 mol% **1**, 2.0 equiv. H_2O_2) enabled the C–H bond α to nitrogen (α-*N*) to be hydroxylated to hemiaminal intermediates (hemiaminal, and hemiaminal acetate from AcOH) in an excellent 82% yield (**4a**). Consistent with slower alcohol oxidation, exposure of alcohol **4a** to identical oxidation conditions afforded 84% hemiaminals with only 10% imide **4b** (Fig. 2b). In contrast, exposure of alcohol **4a** to the forcing conditions afforded predominantly imide **4b** (54%) with only 17% hemiaminals. Under mild oxidation conditions, we additionally observed enhanced chemoselectivities for electron-rich and neutral aromatics and heteroaromatics, likely due to attenuation of similarly higher-energy overoxidation pathways (*vide infra*). Notably, this constitutes among the highest S/C ratio (substrate/catalyst = 200) reported to date for a preparative C(sp^3)–H hydroxylation reaction in a complex setting. The ability to separate the hydroxylated intermediate prior to methylation, while not necessary for alkylation, avoids formation of an inseparable mixture of the methylated product and starting material often observed in direct methylation[17]. Expectedly, Fe(PDP) and Fe(CF_3PDP), previously employed for oxidative α-arylation of aliphatic peptides[28–30] gave a complex mixture of aromatic oxidation products (Extended Data). Mn(PDP), shown to hydroxylate simple linear amides[31], was not reactive enough to promote preparative hydroxylation of **2**, but can be uniquely effective for some sterically hindered substrates (*vide infra*).

A further challenge with an oxidative methylation approach was to identify a way to activate the hemiaminal/hemiacetal towards attack by a nucleophilic methyl source without resulting in either undesirable elimination to the enamine, or attack at other electrophilic moieties in complex substrates (Fig. 1b). The modestly nucleophilic and Lewis acidic nature of organoaluminum reagents suggested they could achieve such selective reactivity. Their high affinity for fluorine coupled to their tolerance of Lewis acids afforded a means of generating reactive iminium or oxonium species from transient C–F or from C–OH bond ionization[32,33]. High functional group tolerance was also expected given organoaluminum reagents' ability to methylate oxoniums at late stages in the presence of other electrophilic functionalities[34].

After significant experimentation abbreviated in Fig. 2a, we arrived at a scalable general procedure employing either diethylaminosulfur trifluoride (DAST) or boron trifluoride diethyl etherate (BF_3•OEt_2) as hydroxyl activators for iminium formation with $AlMe_3$ as an inexpensive, commercial methylating reagent. Thermally stable bis(2-methoxyethyl)aminosulfur trifluoromethanesulfonate (Deoxo-Fluor) may also be used. In general, the fluorine-assisted methylation strategy should be used in substrates containing Lewis basic or electrophilic functional groups, while ones lacking such functionality can be methylated via the BF_3 activation strategy (Extended Data). When unreacted hemiaminal acetate is observed, esterification of the hemiaminal by trifluoroacetic anhydride (TFAA) and subsequent activation of both esters with trimethylsilyl triflate (TMSOTf) to furnish the iminium can be employed[34]. The capacity to vary the ionization method with $AlMe_3$ is critical to the broad scope of this methylation, providing a facile handle to tune reactivity and/or selectivity for a given substrate in cases where unreacted hemiaminal intermediates or enamine byproducts are observed (*vide infra*).

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Alternative activation modes with $AlMe_3$ and methylating reagents with DAST were examined (Extended Data). In hemiaminals, base-mediated formation of an activated C–O bond (i.e., mesylation) gave predominantly elimination (Fig. 2a). Grignard reagents, even at cryogenic temperatures, afford diminished yields relative to $AlMe_3$, likely due to poor functional group tolerance. Although ineffective for methylation of heterocyclic substrates, these reagents can be used to effect methylation in challenging linear secondary amine and carbocyclic substrates (*vide infra*, **51**, **53**).

We explored oxidative methylation for its capacity to methylate a collection of twenty-two compounds comprising ten different heterocyclic cores commonly found in pharmaceuticals (Fig. 3). A gram-scale methylation of **2** was successfully done in 71% yield via DAST activation; an ethyl group could also be installed using commercial triethylaluminum (**5**, 51%). Methylated δ-lactam **6** was isolated in 58% yield; analogous to the γ-lactam, under more forcing oxidation conditions δ-lactam gave predominantly imide (60%). For amide **2**, methylated **3** was observed in preparative yields with both DAST and BF_3 ionization (Fig. 2a). However, in oxazolidinones, housing more labile carbonyls, fluorination with DAST furnished significantly higher yields (**7**, 55% versus 10% with BF_3, Extended Data; **8**, 63%). Pyrrolidine, the fifth most common nitrogen heterocycle in drugs[35,36], undergoes hydroxylation with no significant over-oxidation to pyrrolidinone, followed by BF_3-promoted methylation to afford mono-methylated product **9** in 54% yield. Critical for late-stage derivatization and orthogonal to most radical processes, high site-selectivity for methylation at the less sterically hindered methylene site was observed in substrates bearing more activated tertiary (3°) aliphatic, 3° benzylic, and 3° α-carbonyl C–H bonds to afford products in preparative yields (**10-13**). Full stereoretention was measured with chiral substrates leading to **12** and **13**, indicating that the high regioselectivity is attributed to catalyst control of Mn(CF_3PDP) **1** in the C–H cleavage step. Methyl ester, ketone, acetate, and nitrile, not well tolerated with strongly nucleophilic methylation reagents, were maintained using DAST activation/$AlMe_3$ methylation (**12-15**). Methylation on a 3-phenylpyrrolidine derivative proceeded regioselectively at the methylene site distal from the phenyl group, furnishing the 5-methylated product **16** in useful yield. Such chemoselectivity for electron neutral aromatics has not been previously demonstrated: at higher catalyst loadings, **1** afforded poor yields and chemoselectivities[27].

In piperidines, the most common nitrogen heterocycle in small molecule drugs[35,36], both DAST and BF_3 activation should be tried: enamine formation competes strongly with methylation and is highly dependent on both the substrate and the mode of hemiaminal activation (Fig. 3). For example, a pipecolic acid derivative gave 2% of the methylated product with 60% enamine byproduct under DAST activation, whereas the BF_3 activation furnished **17** in 47% overall yield. Alternatively, methylation of piperidinyl-2-methyl acetate using BF_3 did not fully convert the hemiaminal to methylated product, whereas DAST activation afforded **18** in 64% yield. Gamma-substituted piperidines are prevalent structures in drugs, such as in paliperidone and paroxetine. An *N*-nosyl intermediate in the synthesis of paliperidone was selectively methylated using the DAST protocol to give **19** in 37% yield with no protection of the benzisoxazole ring γ to nitrogen. However, methylation of γ-(4-bromophenyl)piperidine with DAST resulted predominantly in enamine formation, while the

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BF_3 activation strategy affording 39% yield of methylated **20**. Notably, all piperidines furnished a single observed methylated diastereomer, likely as a result of the rigid half-chair conformation of the iminium intermediate[37].

Other simple cyclic amines, such as azepane, azabicycloheptane, and decahydroquinoline, were selectively methylated using the BF_3 activation protocol α-*N* to afford 40%-46% overall yields of mono-methylated products **21-23**. Tetrahydroisoquinoline, among the top 20 nitrogen heterocycles in FDA-approved drugs[36], was oxidatively methylated using BF_3 activation in good yields for both a brominated and an unsubstituted aromatic structure (**24**, 51%; **25**, 50%), with lower yields observed using DAST activation. In contrast to the majority of radical based oxidation methods that oxidize isochromans to isochromanones, under Mn(CF_3PDP) **1** catalysis little over-oxidation is observed. 6,8-Dibromoisochroman was oxidatively methylated using DAST/$AlMe_3$ in 74% yield (**26**); BF_3 activation for these types of oxygen heterocycles afforded ring-opening products[38].

We explored the ability of highly site- and chemoselective Mn(CF_3PDP) **1** catalyzed C–H hydroxylation, coupled to a Lewis-acid/fluorine-promoted methylation, to provide a general method for installing methyl groups directly into the hydrocarbon cores of complex, bioactive molecules, thereby avoiding lengthy and costly *de novo* synthesis (Fig. 4)[1,9,10]. Cromakalim acetate, a potassium channel activator housing a γ-lactam with tertiary and secondary hyperconjugatively activated α-*N* C(sp^3)–H bonds, underwent oxidative methylation at the less activated but more sterically accessible secondary site in good yield (**27**, 51%). The acetate could be readily removed to furnish methylated cromakalim **28** in 85% yield. The methyl ester of indoprofen, an anti-inflammatory drug investigated for spinal muscular atrophy[39], was oxidatively methylated at its central isoindolinone core in synthetically useful yields (**29**, 33%). The enhanced chemoselectivity of oxidative methylation with **1** under reduced loadings is evident when comparing with results at higher loadings (10 mol%), where **29** was obtained in diminished yields (7%) due to poor chemoselectivity. Chloroindoprofen methyl ester, a derivative with decreased electron density on the aromatic ring, undergoes oxidative methylation in higher yields (**30**, 55%). Fenspiride, an antitussive drug, was oxidatively methylated in a useful overall yield (**31**, 24%) at a methylene site adjacent to the quaternary center of an unprotected spiro-oxazolidinone, using (*S,S*)-Mn(PDP)(SbF_6)$_2$ catalyst that is less sensitive to sterics[27]. The basic piperidine nitrogen of fenspiride was protected with HBF_4 and rendered a strong electron-withdrawing group, deactivating a distal benzylic site and three α-*N* sites towards C–H oxidation[40]. Notably, SET reactions proceeding via basic amine catalysis (e.g. quinuclidine) are not amenable to this kind of nitrogen protection strategy and therefore do not undergo remote C–H functionalizations[17,24]. A derivative of pozanicline, a neuroprotective drug evaluated for ADHD treatment[41], undergoes α-*N* oxidative methylation at the pyrrolidine in useful yield and diastereoselectivity (**32**, 34%, 6:1 dr). The HBF_4 protection deactivates the basic pyridine moiety and its proximal ethereal sites from oxidation with **1**. While DAST activation produced similar yields, a higher diastereoselectivity was obtained with BF_3 activation (6:1 vs. 3:1), possibly due to different iminium counterions (Fig. 1b). The nosyl group on pyrrolidine, a convenient chromophoric protecting group for secondary amines, was readily removed using thiophenol and

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subsequently protected with tert-butyloxycarbonyl (Boc) to afford **33** in 57% overall yield. Underscoring the unique chemoselectivity of this method, a derivative of the antidepressant diclofensine was oxidatively methylated at its tetrahydroisoquinoline core to afford **34** in useful yield despite the presence of a very electron rich methoxyphenyl. Mild, reductive desulfonation followed by reductive amination furnished Me-diclofensine **35** in 82% yield. The antidepressant drug citalopram, upon HBF_4 protection of the tertiary amine, is oxidatively methylated at its dihydroisobenzofuran core to afford **36**. DAST activation was used on the majority of these densely functionalized substrates whereas BF_3 activation was more effective on the tetrahydroisoquinoline core.

A precursor to pyrroloisoquinoline, a prevalent structure in compounds with neurotransmitter uptake inhibitor properties[42], undergoes selective oxidative methylation at the less sterically hindered methylene site, versus the more activated tertiary, benzylic site, to furnish **37** (44% yield, Fig. 4a). Oxidation of a carbamate precursor to antibiotic tedizolid furnished substantial amounts of hemiaminal acetate that could be methylated in a useful overall yield under the TFAA/TMSOTf-assisted methylation (**38**, 44%). This method is operationally facile and can be performed on gram scale with no loss in efficiency (45% yield). Fluorination afforded lower yields of methylated product **38** due to unconverted hemiaminal acetate. The core piperidine of a paroxetine precursor and metabolite[43] was oxidatively methylated in useful overall yields (**39**, 34%) preferentially at the less sterically hindered methylene site remote from the 3-acetoxymethyl group. Nosyl deprotection and subsequent Boc protection afforded **40** in 86% yield. A piperidine derivative of the anti-inflammatory drug celecoxib was mono-methylated to afford **41** in good overall yield in the presence of an oxidatively labile tolyl group and pyrazole, both tolerated during C–H oxidation with **1** and requiring no protection. In these piperidine substrates, BF_3 activation was effective in furnishing methylated products.

Methylation of proline-based di-, tri-, and tetrapeptides proceeded with good overall yields and mass balances (**42**, **43**, **44**) with **1** under fluorine-assisted oxidative methylation conditions (Fig. 4a). Deoxo-Fluor may be used in substrates like tetrapeptide **44**, where isolation from the polar byproducts of DAST is challenging. Although effective in promoting arylation of peptides with electron rich aromatic nucleophiles, BF_3 activation in the $AlMe_3$ methylation of peptides afforded complex mixtures, likely arising from activation of the amide carbonyls[30]. Ambroxide, a naturally occurring terpenoid, also undergoes selective oxidative methylation using DAST at a methylene site α to oxygen on its tetrahydrofuran ring to afford **45** in 32% yield (with 19% of sclareolide lactone). The use of BF_3 in this case promoted ring-opening. Significantly, Fe(PDP), ruthenium-mediated oxidation, and **1** under forcing conditions all afforded sclareolide lactone as the major product isolated (see SI)[10,21,28].

The sultam ring in an advanced intermediate of an RORc inverse agonist **46** (Fig. 4b) was oxidatively methylated with **1** using TFAA/TMSOTf activation/$AlMe_3$ to afford **47** as the *syn*-diastereomer. Other activation modes, such as BF_3, resulted in deleterious elimination pathways. Notably, an oxidatively labile phenyl moiety and a doubly activated benzylic methylene site were tolerated. Previous installation of the *syn*-methyl group afforded a 13-fold increase in RORc SRC1 selectivity relative to the unmethylated version; however, it

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required a six-step *de novo* synthesis proceeding in 1.4% overall yield[5]. This analog and others are now accessible via cross-coupling with methylated intermediate **47**.

Tedizolid, a commercial oxazolidinone antibiotic for acute bacterial skin infections, bears numerous oxidatively sensitive functional groups such as a pyridine, tetrazole, and an *N*-methyl (Fig. 4c). Mn(CF_3PDP) **1** oxidation (2 mol%) of tedizolid acetate **48** proceeded in *ca.* 53% yield of oxidized products (3:1 hemiaminal/acetate) with no protection of the dense nitrogen functionalities. The significant challenge was to identify a procedure to install the methyl group from the hemiaminal intermediates. Activation via fluorination furnished primarily eliminated products not observed on the simpler core structure (**38**, Fig. 4a), while BF_3 activation resulted in side reactions. However, under TFAA/TMSOTf activation, elimination was suppressed and the methylated product **49** was obtained in a remarkable 40% overall yield, 74% per step, comparable to that of the simpler precursor **38**. Deprotection of the acetate in 92% yield afforded Me-tedizolid **50**, an interesting candidate for future biological evaluation given that a 9-fold boost in potency has been reported for similar oxazolidinone cores with methylation at the same position (Fig. 1a)[44].

We questioned if the scope of this reaction could be extended beyond heterocycles, and found that oxidative C–H methylation is not restricted to substrates that can form iminium or oxonium intermediates: promising reactivity has been observed for both imines and remote alcohols generated via C–H hydroxylation with **1**. An $S1P_1$ antagonist, whose benzylic and aromatic methylations afforded a 2135-fold potency increase[6], was methylated in its methyl ester form (**51**, Fig. 4d). While oxidation of the antagonist was successful without need for protection of the aniline motif, the resulting imine was much less reactive than an iminium and required a stronger nucleophile than $AlMe_3$. In this case, we found that methylmagnesium bromide at cryogenic temperatures, with TMSOTf activation of the imine, produced the methylated product without eroding the amide and ester functional groups (**52**, 14%, 52% per step).

At higher catalyst loadings, Mn(CF_3PDP) **1** is an effective catalyst for methylene C–H bond hydroxylations[27]. Abiraterone analog **53** was hydroxylated in *ca.* 32% yield (with 16% ketone) in one step, without recycling the starting material as required in Fe(CF_3PDP) catalysis (Fig. 4e)[40]. In carbocyclic substrates, displacement of a C–F bond or ionization with a Lewis acid is difficult; however, mesylates of such aliphatic alcohols are stable and can be activated by $AlMe_3$ to undergo substitution[45]. By replacing fluorination with mesylation, **53** was successfully methylated as a single observed diastereomer (**54**, 15% overall yield, 53% per step), likely through a carbocation intermediate. To the best of our knowledge, this is the first method that enables such remote methylation at unactivated C(sp^3)–H bonds. The discovery of this reactivity underscores the importance of developing methylene oxidations that afford predominately alcohol products.

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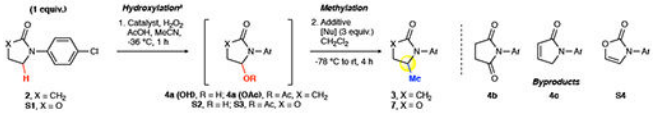
Extended Data

Extended Data Table 1 |

Reaction Optimization.



Entry	Substr.	Catalyst	Loading (mol%)	Additive	[Nu]	4a (OH)/ S2 (%)	4a (OAc)/ S3 (%)	3/7 (%)	4b (%)	4c/ S4 (%)	rsm (%)
Oxidation											
1[b]	**2**	Fe(PDP)	3 x 5	-	-	<5[k]	0	-	<5[k]	-	0
2[c]	**2**	Fe(CF_3PDP)	3 x 5	-	-	8[k]	0	-	6[k]	-	0
3[d]	**2**	Mn(PDP) $(OTf)_2$	1	-	-	12	0	-	0	-	75
4	**2**	Mn(PDP) $(SbF_6)_2$	1	-	-	28	7	-	<5[k]	-	35
5[e]	**2**	Mn(CF_3PDP) **1**	10	-	-	13[k]	10	-	41	-	0
6	**2**	**1**	1	-	-	51	21	-	9	-	0
7	**2**	**1**	0.5	-	-	64	18	-	<5[k]	-	4
Methylation											
8[f]	**2**	**1**	0.5	BF_3•OEt_2	$AlMe_3$	<5[k]	0	63	<5[k]	0	11
9[f]	**S1**	**1**	0.5	BF_3•OEt_2	$AlMe_3$	11	5	10	-	4	27
10[g]	**S1**	**1**	0.5	DAST	$AlMe_3$	0	14[k]	55	-	0	16
11[g]	**2**	**1**	0.5	DAST	$AlMe_3$	0	0	64	<5[k]	0	12
12[g]	**2**	**1**	0.5	Deoxo-Fluor	$AlMe_3$	0	0	61	6	0	5
13[h]	**2**	**1**	0.5	TFAA/ TMSOTf	$AlMe_3$	0	0	51	<5[k]	14	9
14[h]	**S1**	**1**	0.5	TFAA/ TMSOTf	$AlMe_3$	0	0	46	-	20	13
15[i]	**2**	**1**	0.5	MsCl/ Et_3N	$AlMe_3$	15	0	0	<5[k]	39	6
16[g]	**2**	**1**	0.5	DAST	$ZnMe_2$	17	9	0	11	0	14
17[g,j]	**2**	**1**	0.5	DAST	MeMgBr	24	<5[k]	24	<5[k]	0	9

[a] General oxidation (unless otherwise noted): **2** (0.3 mmol), catalyst (x mol%, (*R,R*) and (*S,S*) used interchangeably), AcOH (15 equiv.), MeCN (0.5 M), −36 °C; H_2O_2 (2 equiv.) in MeCN (3.75 mL) syringe pump 1 h. Mixture passed through silica plug, EtOAc flush, concentrated prior to isolation or methylation. Isolated product yields.

[b] Procedure ref. 28.

[c] Procedure ref. 29.

[d] Procedure ref. 31.

[e] 5 equiv. H_2O_2.

[f] General BF_3 alkylation: crude in CH_2Cl_2 (0.2 M), −78 °C, $AlMe_3$ (3 equiv.) and BF_3•OEt_2 (2 equiv.) sequentially added, stirred 1 h; room temperature (rt) for 3 h.

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[g] General fluorine alkylation: crude in CH_2Cl_2 (0.2 M), fluorine additive (1 equiv.) added at −78 °C; rt for 1 h; cooled to −78 °C, nucleophile (3 equiv.) added, stirred 2 h; rt for 1 h.

[h] General TMSOTf alkylation: crude in CH_2Cl_2 (0.2 M), TFAA (1 equiv.) added, stirred 1 h; cooled to −78 °C, $AlMe_3$(3 equiv.) and TMSOTf (1 equiv.) sequentially added, stirred 2 h; rt for 1 h.

[i] Crude in CH_2Cl_2 (0.2 M), MsCl (1 equiv.) and Et_3N (1 equiv.) added, stirred 1 h; washed $NaHCO_3$, dried, reduced; redissolved in CH_2Cl_2, $AlMe_3$ (3 equiv.) added at −78 °C, stirred 2 h; rt for 1 h.

[j] MeMgBr (3 equiv.) added at −78°C, stirred 3 h.

[k] Yield by crude ^{1}H NMR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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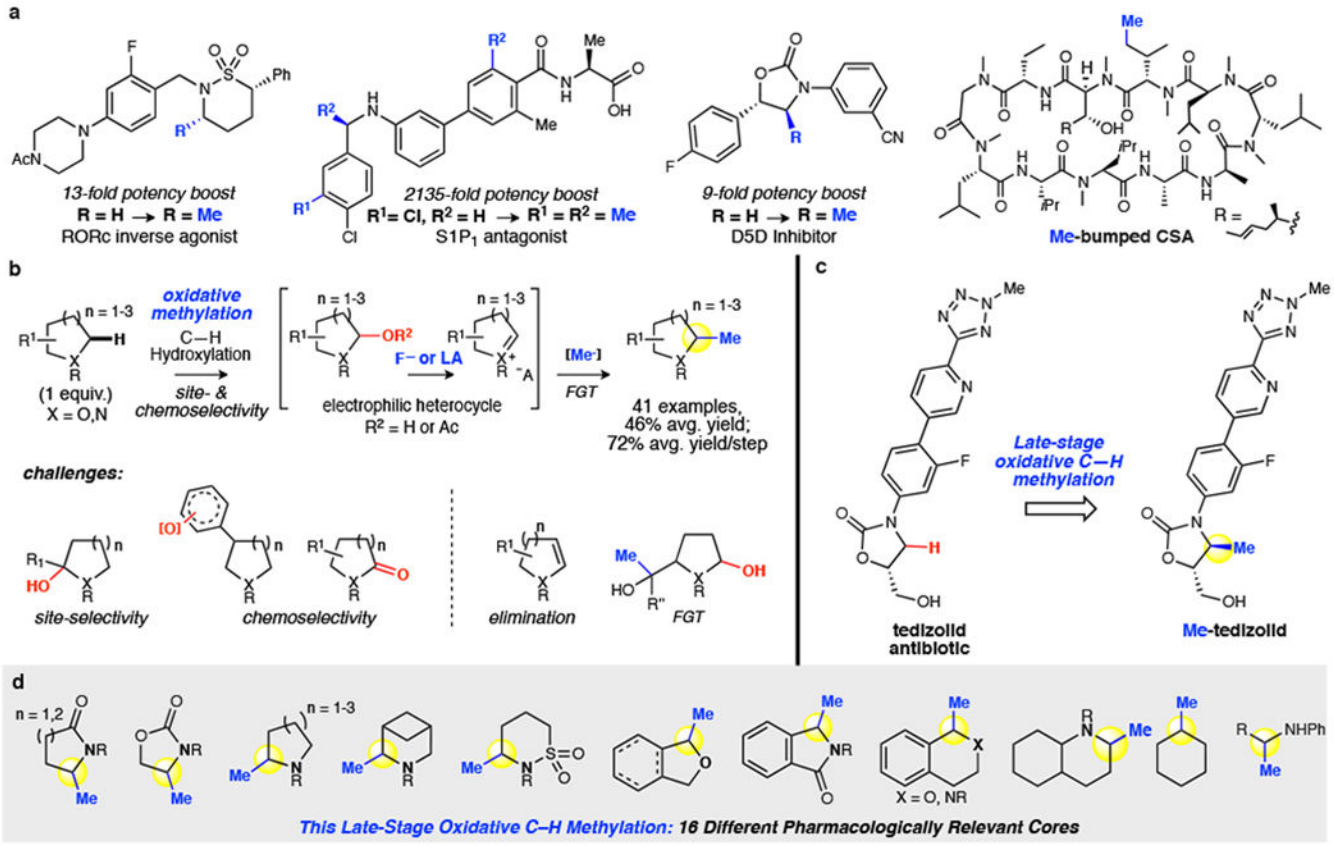

Fig. 1 |. C(sp^3)–H methylation.

a, The magic methyl effect boosts potency of drugs and furnishes biological probes. **b**, This oxidative methylation proceeds through an electrophilic intermediate. Challenges included over-oxidation, unselective oxidation, elimination and unselective methylation pathways. **c**, Late stage oxidative methylation of antibiotic tedizolid. **d**, Oxidative C-H methylation is demonstrated on 16 different pharmaceutically relevant cores. Using only 1 equivalent of substrate, methylation proceeds site-selectively and with functional group tolerance to afford preparative yields in 41 examples (including 18 complex bioactive molecules).

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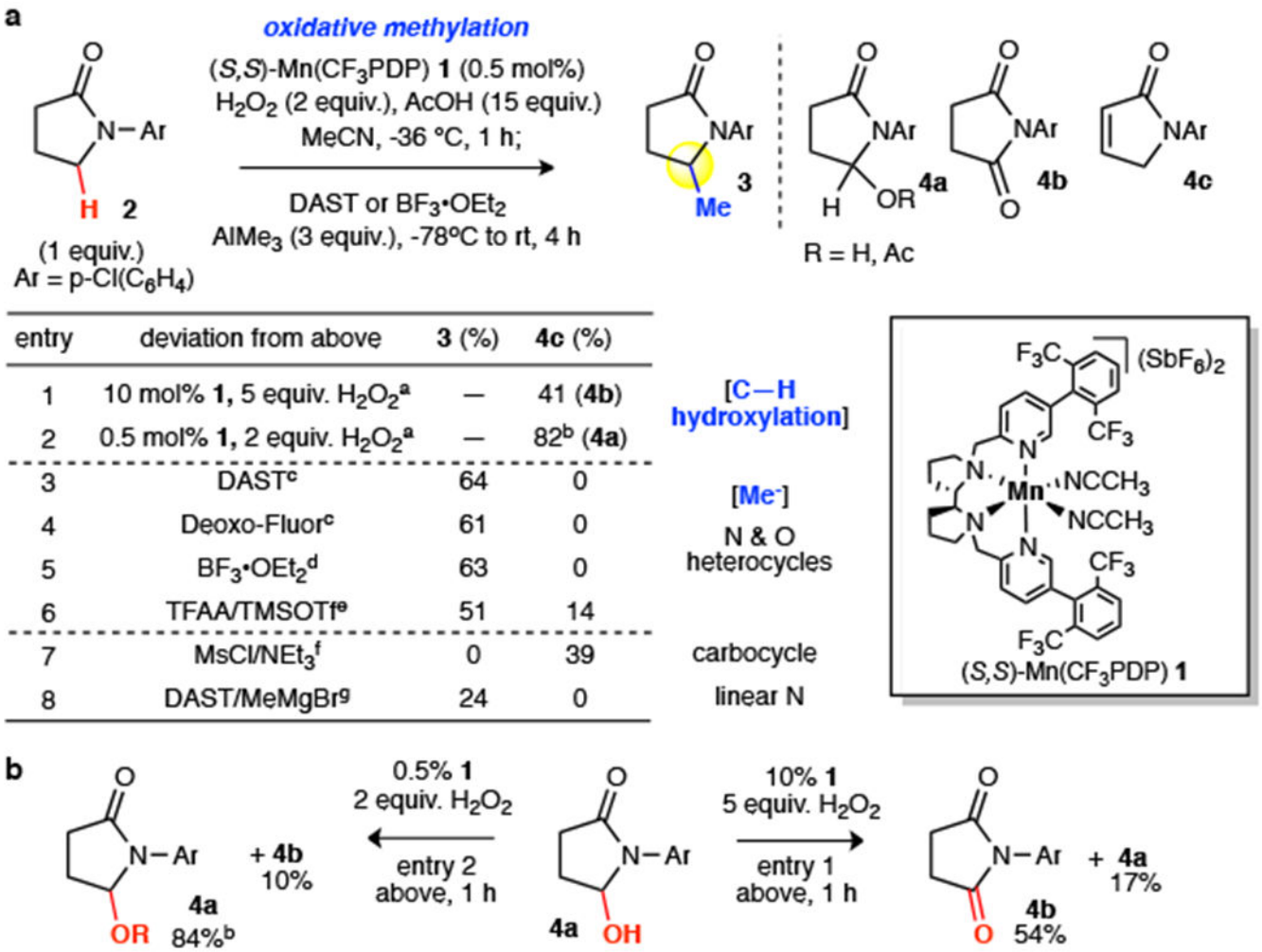

entry	deviation from above	3 (%)	4c (%)
1	10 mol% **1**, 5 equiv. H_2O_2[a]	—	41 (**4b**)
2	0.5 mol% **1**, 2 equiv. H_2O_2[a]	—	82[b] (**4a**)
3	DAST[c]	64	0
4	Deoxo-Fluor[c]	61	0
5	BF_3•OEt_2[d]	63	0
6	TFAA/TMSOTf[e]	51	14
7	MsCl/NEt_3[f]	0	39
8	DAST/MeMgBr[g]	24	0

Fig. 2 |. Reaction development.

a, Optimization of the oxidative methylation reaction. For achiral substrates, (*R,R*)- and (*S,S*)-**1** can be used interchangeably. **b**, Exposure of hemiaminal to mild C–H hydroxylation developed here (0.5 mol% **1**, 2 equiv. H_2O_2) gives little overoxidation to the imide. The previous forcing condition (10 mol% **1**, 5 equiv. H_2O_2) results in imide as the major product. [a]No methylation. [b]Mixture of hemiaminal (64%-71%) and hemiaminal acetate from AcOH (13%-18%). [c]1 equiv. [d]2 equiv. [e]TFAA (1 equiv.), TMSOTf (1 equiv.). [f]MsCl (1 equiv.), NEt_3 (1 equiv.), $NaHCO_3$ wash; $AlMe_3$ (3 equiv.), −78 °C, 2 h; rt 1 h. [g]MeMgBr (3 equiv.), −78°C, 3 h.

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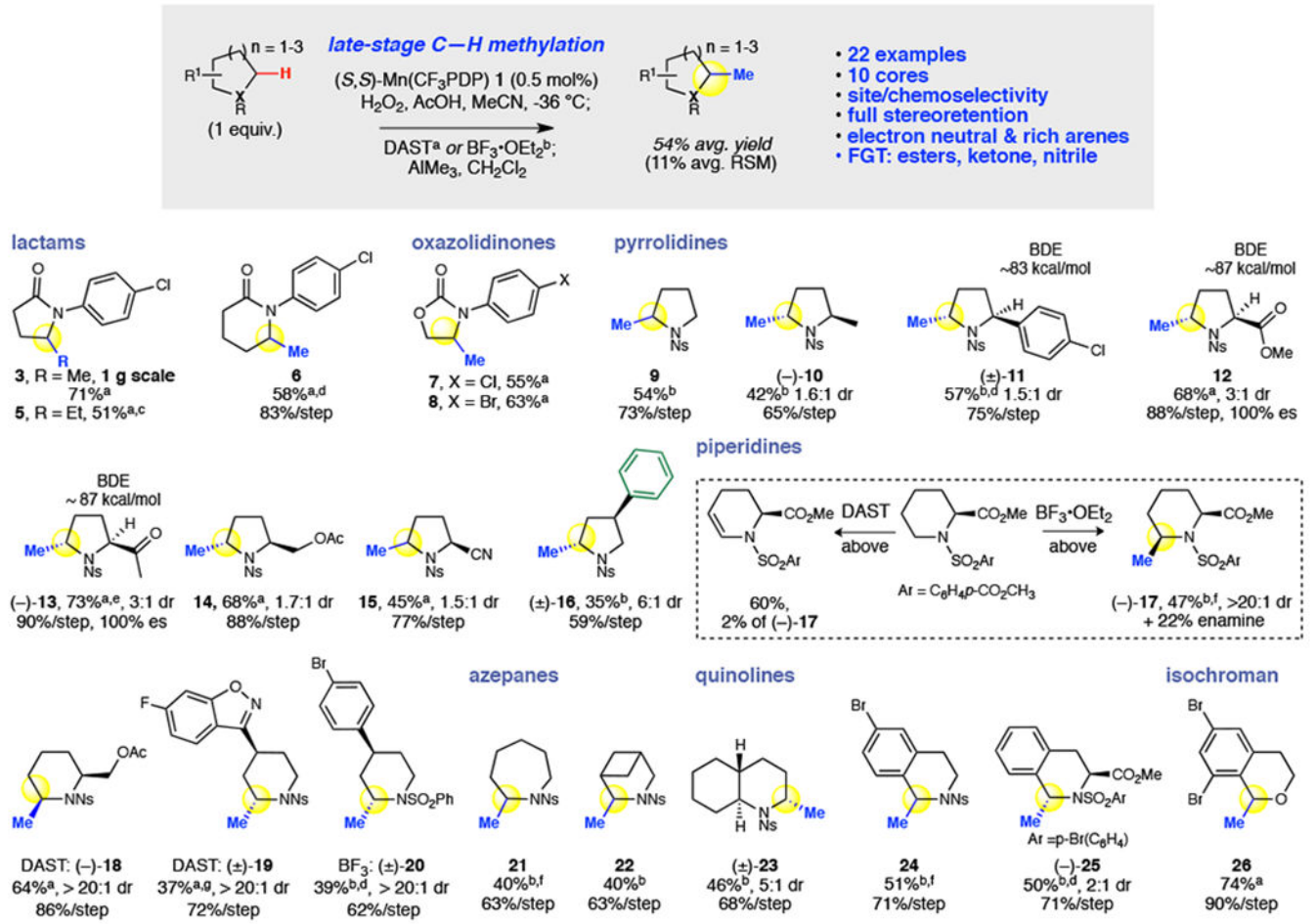

Fig. 3 |. Ten different heterocyclic cores, commonly found in pharmaceuticals, were explored in the Mn(CF$_3$PDP) 1-catalyzed C–H hydroxylation and methylation.

Twenty-two heterocycles including lactams, oxazolidinones, pyrrolidines, piperidines, azepane, azabicycloheptane, quinolines, and isochroman were oxidatively methylated in preparative overall yields (54% average) using limiting substrate. General oxidation: substrate, catalyst (0.5 mol%), AcOH in MeCN, −36 °C; H_2O_2 (2 or 5 equiv.) in MeCN syringe pump 1 h. Mixture passed through silica plug, EtOAc flush, concentrated prior to isolation or methylation. For insoluble substrates, CH_2Cl_2 added to MeCN and/or 0 °C. [a]DAST Activation: crude in CH_2Cl_2 (0.2 M), DAST (1 equiv.) added at −78 °C; room temperature (rt) for 1 h; cooled to −78 °C, $AlMe_3$ added, stirred 2 h; rt for 1 h. [b]BF_3 Activation: crude in CH_2Cl_2 (0.2 M), −78 °C, $AlMe_3$ (3 equiv.) and BF_3•OEt_2 (2 equiv.) sequentially added, stirred 1 h; rt for 3 h. [c]Triethylaluminum. [d]2 mol% (*S,S*)-**1**. [e]$AlMe_3$ −78 °C, 3 h. [f]1 mol% (*S,S*)-**1**. [g]For facile purification, hemiaminal isolated before methylation. 10 mol% (*S,S*)-**1**, rt, starting material recycled 1x.

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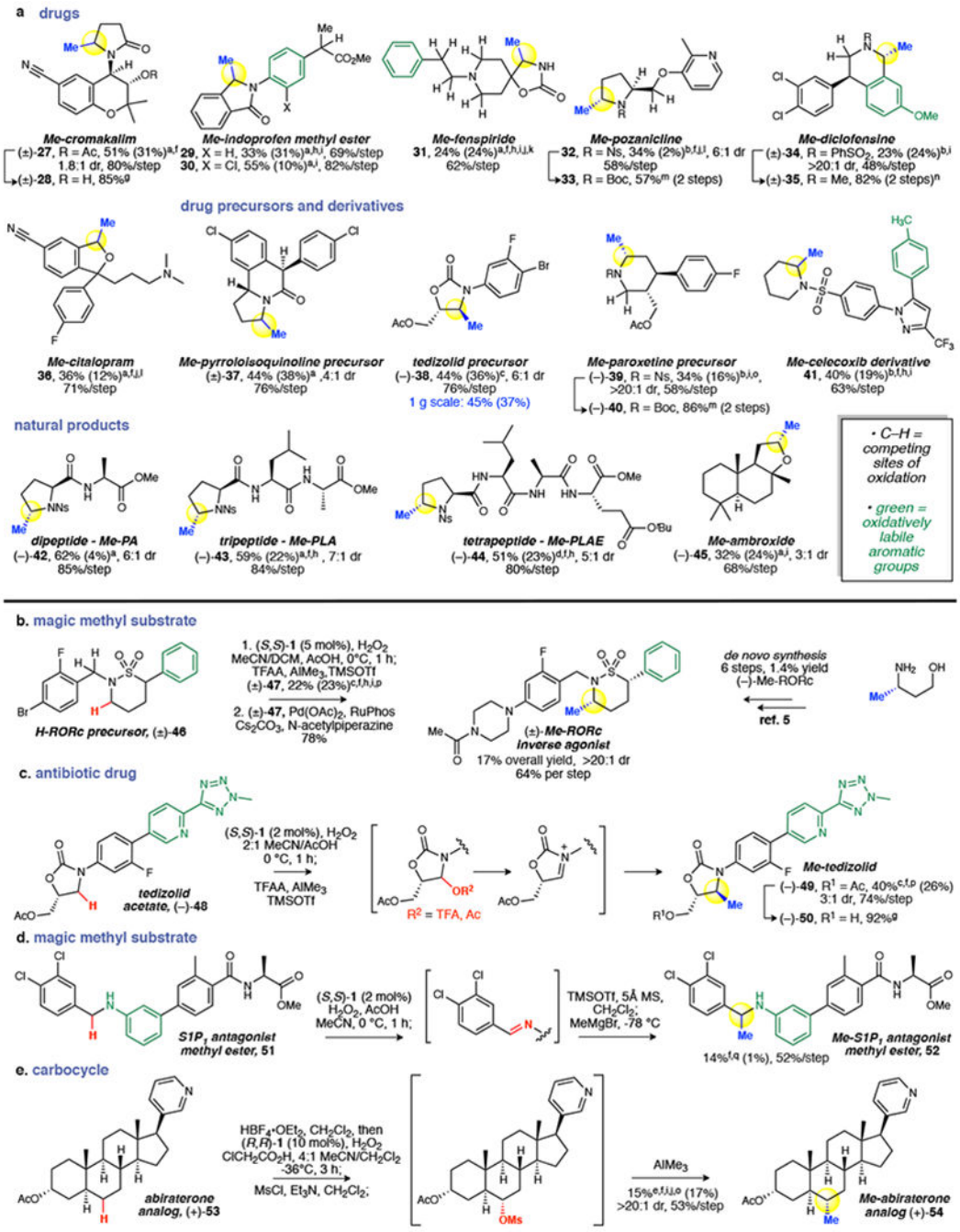

Fig. 4 |. Application of oxidative methylation for late stage functionalization.

a, Selective methylation of drugs, drug precursors, intermediates and natural products underscores the power of this method for late stage applications. Generally, 0.5 to 5 mol% (*S,S*)-**1** and 2 or 5 equiv. H_2O_2 were used for oxidation. Higher catalyst and oxidant loadings were applied when conversions were low. **b**, Methylation of an RORc inverse agonist precursor rapidly furnishes the analogue with 13-fold potency boost. **c**, Methylation of antibiotic tedizolid acetate furnishes Me-tedizolid. **d**, Methylation of linear aniline in $S1P_1$ antagonist methyl ester occurs at a position where magic methyl effect was observed to

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contribute to a 2135-fold potency boost. **e**, Remote methylation of a carbocycle on an abiraterone analog. [a]DAST activation. [b]BF_3 activation. [c]TMSOTf activation: TFAA, rt, 1 h; cooled to −78 °C, $AlMe_3$ and TMSOTf sequentially added, 2 h; then rt, 1 h. [d]Deoxo-Fluor activation. [e]Mesylation activation: MsCl and Et_3N added, rt, 1 h; $NaHCO_3$ wash, dried, condensed; redissolved in CH_2Cl_2, $AlMe_3$ added at −78 °C, stirred 2 h; then rt, 1 h. [f]Oxidation intermediates isolated before methylation. [g]1 M NaOH/MeOH. [h]Starting material recycled 1x. [i]For insoluble substrates, CH_2Cl_2 added to MeCN and/or 0 °C. [j]HBF_4 protection, ref. 40. [k]10 mol% (*S,S*)-Mn(PDP)$(SbF_6)_2$. [l]10 mol% (*S,S*)-**1**. [m]PhSH, Cs_2CO_3; Boc_2O. [n]Mg, NH_4Cl; formaldehyde, formic acid. [o]10 mol% (*RR*)-**1**. [p]2 equiv. TMSOTf. [q]TMSOTf (1.2 equiv.), 0 °C, 1 h, then MeMgBr (3.0 equiv.) −78 °C, 4 h, repeated once.