Regiodivergent Metalation of Pyridines Using Mixed TMP-Titanate and TMP-Fe-Titanate Bases

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Abstract

Functionalization of pyridine rings via direct metalation remains challenging because of issues pertaining to functional group compatibility under mild conditions, regiodivergence and coupling reactions of 2-pyridyl organometallics. Here we report two novel, practical and readily available TMP-based metallic reagents: Ti-1·2(TMPMgCl·LiCl) [A] and Ti-1·$FeCl_2$ ·2(TMPMgCl·LiCl) [B], which enabled the rapid metalation of various unactivated and functionalized pyridines with high functional group tolerance and regioselectivity at room temperature. Notably, these two reagents exhibited unprecedented regiodivergence; A selectively metalated 2- or 3-functionalized pyridines at C6 position irrespective of the classic ortho direction of 2- and 3-position functional groups, whereas B promoted the metalations ortho to the functional groups. Moreover, under the mediation of A, the regiodivergent Pd and Fe-catalyzed deprotonative cross couplings of pyridines were easily achieved using simple catalyst (i.e., $Pd(dba)_2/PPh_3$ and $FeCl_3$/TMEDA) and without transmetalation, thereby providing a solution to the cross-coupling problem of 2-pyridyl organometallics. Preliminary DFT calculations suggest that the metalation using A should involve magnesiation while that using B may involve ferration promoted by Fe/Ti synergism. These findings not only provide a powerful tool for the direct functionalization of pyridines, but also allow the late-stage diversification of natural products and drugs, as demonstrated for nicotine and boscalid.

Introduction

Regioselective direct metalation of (hetero)aromatics using metal amide bases, known as directed *ortho*-metalation, has become an important tool for functionalizing these compounds. Although classical lithiation demonstrates a strong metalation ability and has been widely employed,[1] the high reactivities of organolithium reagents necessitate cryogenic conditions for both the lithiation process and the subsequent reactions of the resulting aryl lithium species. In addition, this approach often shows unsatisfactory functional group tolerance. To address this, a series of mixed metal TMP (2,2,6,6-tetramethylpiperidyl) amides such as $^iBu_3Al(TMP)Li$,[2] $R_2Zn(TMP)Li$,[3] $RCu(CN)(TMP)Li_2$,[4] TMPMCl·LiCl/TMP_2M·2LiCl (M = Mg, Zn);[2,5] and TMP_2Fe·4LiCl[6] have been developed and employed, often with milder reaction conditions and improved selectivity. Nevertheless, the preparations of some these reagents still require sensitive organolithium reagents, and cryogenic conditions are also required during their reactions.

Pyridine and quinoline scaffolds are commonly found in natural products, drugs, ligands, and materials science. For example, pyridine is the second most common nitrogen heterocycle among all U.S. FDA approved pharmaceuticals (Fig. 1A).[7] Consequently, regio- and chemoselective functionalization of these privileged azaheterocycles via direct metalation and electrophilic trapping is of particular importance but remains a challenging task in organic synthesis. To date, numerous reports have described the direct lithiation of pyridine ring under cryogenic conditions, which often leads to an unsatisfactory functional group compatibility.[8] In addition, the metalation of pyridines using the aforementioned mixed metal TMP amides still faces some challenges. For example, the reagents for metalating unactivated pyridines (e.g., pyridine or 4-Me_2N-pyridine) are limited (Fig. 1B).[9,10] In addition, although the regiodivergent metalation of pyridines is an attractive synthetic route to valuable isomeric pyridines, a general protocol for the regiodivergent metalation of pyridines remains elusive, especially in the context of regioselective metalations that can override the classic *ortho* direction of some functional groups (e.g., ester, amide and cyano) (Fig. 1B). Previous studies have focused largely on selective C2-H or C4-H metalation of 3-functionalized pyridines.[8,10] Furthermore, the coupling reactions of 2-pyridyl organometallics have been problematic,[11] and the magnesiated and lithiated pyridines obtained using TMP bases often require transmetalation with $ZnCl_2$ prior to performing the Pd-catalyzed coupling reaction.[10,12]

Considering our previous study on Fe/Ti synergism and related reactions,[13] we envisage that the combination of titanate and titanate/$FeCl_2$ with TMPMgCl(·LiCl) could produce mixed metal TMP amides without employing sensitive organolithiums, while potentially exhibiting enhanced chemo- and regioselectivity by virtue of the advantages of titanium reagents and Fe/Ti synergism. Herein, we report two novel and practical mixed TMP amides: **Ti-1**·2(TMPMgCl·LiCl) [**A**] and **Ti-1**·$FeCl_2$·2(TMP MgCl·LiCl) [**B**]. They were obtained by the combination of readily available TMPMgCl·LiCl, **Ti-1** and $FeCl_2$, and can directly metalate unactivated and functionalized pyridines selectively and rapidly at room temperature. Importantly, these two reagents exhibit unique and broadly applicable regiodivergence in the direct metalation of various pyridines. Furthermore, under the mediation of **A**, the regiodivergent Pd- and Fe-catalyzed deprotonative cross couplings of pyridines using simple catalysts proceeded without transmetalation, providing a practical solution to the problem associated with the couplings of 2-pyidyl metallic reagents (Fig. 1C). Notably, both reagents solidified following solvent evaporation and demonstrated remarkable stability when stored in sealed containers under an argon atmosphere at ambient temperature for up to one week, showing only a slight decrease in yield (Fig. 1C). Additionally, the aqueous workup of the reactions employing titanates is known to generate a milky TiO_2 precipitate, which is very difficult to filter.[14] In stark contrast, the use of **Ti-1** (Fig. 1C) in present system facilitated the reaction workup. Hence, we expect that the development of these two reagents and related reactions will provide a new and practical approach to the functionalization of pyridine and related heterocyclic rings and promote research into the chemistry of mixed metal ate TMP amides.

Results and Discussion

Discovery and Optimization. Two unactivated pyridine compounds (pyridine and N, N-dimethylpyridin-4-amine) were selected as substrates, and their metalations were explored using the mixed TMP amides obtained by combining various titanates with TMPMgCl(·LiCl) and $FeCl_2$/TMPMgCl(·LiCl) (for additional details, see Supporting Information). It was discovered that **A** [tentatively formulated as **Ti-1**·2(TMPMgCl·LiCl)] and **B** [tentatively formulated as **Ti-1**·$FeCl_2$·2(TMPMgCl·LiCl)] successfully metalated the two pyridines at room temperature. Subsequently, the metalated pyridine intermediates generated in the presence of **A** were trapped with I_2, whereas those obtained using **B** were trapped with I_2 and BnCl (Table 1). From the obtained results, it was evident that **A** successfully metalated both pyridine compounds within 40 minutes at room temperature, providing the desired products in high yields (entries 1–2 in Table 1). In contrast, almost no metalation was observed using TMPMgCl·LiCl and TMPMgCl in the absence of **Ti-1** (entries 4–5). In addition to the influence of LiCl on the reaction outcome (entries 1, 2 vs 3), the type of titanate also affected the metalation, with **Ti-1** giving the optimal results (entries 6–9). **Ti-1** exists as a readily synthesizable solid with excellent handling and storage properties, while compounds **A** and **B** also exhibit solid-state stability under an argon atmosphere at ambient temperature, thereby significantly improving their practical utility and operational convenience. It was also found that **B** can also metalate the two pyridines within 1h at room temperature (entries 10–14). Replacing $FeCl_2$ with $FeCl_2$/TMEDA did not significantly affect the reaction outcome (entry 13), and it was evident that the Fe/Ti combination in **B** allowed the benzylation to proceed easily without the requirement for external ligands (e.g. TMEDA) and other metals (e.g. Cu(I) or Ni salts)[6] (entries 12–14). Conversely, $FeCl_2$·2(TMPMgCl·LiCl)[6] and $FeCl_2$·2(TMPMgCl) were unable to metalate the pyridine in the absence of **Ti-1** (entries 15 and 16).

Regiodivergent metalation and functionalization of pyridines using reagents A and B. On the basis of the aforementioned findings, we explored the C-H metalation of various substituted pyridines using **A** and **B**, and the results are listed in Fig. 2. These two reagents exhibited good functional group tolerance and high regioselectivity at room temperature. Notably, **A** and **B** demonstrate an intriguing regioselectivity switch, wherein **A** overrides the *ortho* direction of classic directing groups to achieve previously inaccessible C6-H metalation (**2Ac-o** in Fig. 2). Moreover, **B** was found to promote C3-H or C2-H metalation at the adjacent position of the directing groups (**2Bc-o** in Fig. 2). In the case of 2-substituted pyridines, **A** facilitated C6-H metalation at room temperature in the presence of various *ortho*-directing groups, thereby providing a mild and practical method for the synthesis of various 2,6-disubstituted pyridines from readily available 2-substituted pyridines (**2Ac-k**). In contrast, **B** achieved C3-H metalation at room temperature, and various 2,3-disubstituted pyridines were conveniently prepared from simple 2-substituted pyridines (**2Bc-k**). Although neither C6-H nor C3-H metalations (lithiation, magnesiation or zincation) of 2-EtOOC-, 2-NC-, 2-PhCO-, 2-CH_3CO-, 2-CF_3CONH-pyridines have been reported to date;[15] these pyridines were easily metalated using **A** and **B**, and subsequently functionalized by various electrophiles. Ethyl 6-aminopicolinate and derivatives are a class of useful compounds that was previously prepared from 6-methylpyridin-2-amine via a four-step transformation (i.e., acetylation, oxidation, deacetylation and esterification).[16] In this study, **2Ac** was successfully prepared from ethyl picolinate via a C6-H metalation/electrophilic amination strategy using **A**. Contrary to the classic Chichibabin reaction, such amination can be carried out under mild conditions and has been demonstrated to tolerate a variety of sensitive functional groups, while also allowing the introduction of more complex amine groups (see **2Ah**, **2Bh** and **2Bi**). This amination can also be performed at the C3 position using **B**, where C2 substituents that are highly sensitive to aminolysis and nucleophilic amination (e.g. COOEt, CN, F and Cl) are well tolerated (**2Bc**, **2Bd**, **2Bh** and **2Bi**). Furthermore, 6-

benzylpicolinonitrile (**2Ad**) and its analogues are important precursors for the synthesis of chiral ligands and pesticides; and their reported syntheses involve the benzylation of 2-chloropyridine, followed by *N*-oxidation and cyanidation.[17] Notably, our synthesis of **2Ad** only involved the benzylation of the metalated picolinonitrile following its deprotonation by **A**. Owing to the complexation of N atom, the C-H palladiation and rhodiation reactions of 2-benzoylpyridine have been reported to occur at C2' on the benzene ring.[18] Hence, C3-H and C6-H lithiation and magnesiation on the pyridine ring have scarcely been reported. In contrast, C6-H and C3-H metalations on the pyridine ring were facilely accomplished using **A** and **B**, affording **2Ae** and **2Be**, respectively.[19] Considering the CH_3CO group of 2-acetylpyridine readily participates in aldol reaction and alkylation through enolization;[20] it was surprising to discover that this substrate could be directly metalated at the pyridine C6 and C3 positions using **A** and **B**, respectively. Importantly, products **2Af** and **2Bf** were obtained without any modification of the $COCH_3$ group. Moreover, although CF_3CONH can function as an efficient *ortho*-directing group for C-H magnesiation;[21] the metalation of 2-trifluoroacetamidopyridine using **A** occurs selectively at the C6 position, and the highly useful **2Ag** was prepared in a one-pot manner.[22] Alternatively, **B** promotes a regiodivergent C3-H metalation to generate **2Bg**. Although n-BuLi-LDMAE and $TMSCH_2Li$-LDMAE can promote the C6-H lithiation of 2-Cl, 2-F and 2-MeO pyridines,[23] the lithiation required a large excess amount of the base and the reaction of 2-bromopyridine cannot be performed due to Li/Br exchange. Conversely, the use of 0.75 equivalents of **A** resulted in successful C6-H metalation for these pyridines (including 2-bromopyridine) at room temperature, affording various 2,6-disubstituted pyridines (**2Ah-k**). Notably, these results demonstrated the versatility for **A** to selectively metalate pyridines at the C6 position, irrespective of the presence of various *ortho*-directing groups. In contrast, 0.75 equivalents of **B** promoted the room temperature metalation of these pyridines at the C3 position, smoothly affording the corresponding regiodivergent products (**2Ah-k**).[24]

In the case of 3-functionalized pyridines, previously reported regioselective metalation protocols have mainly focused on the regioregulation between the C2 and C4 posiitons. For example, the lithiation of N,N-dimethyl nicotinamide and 3-halopyridines occurs selectively at the C4 position.[24,25] In addition, Knochel et al reported regioswitchable metalation of 3-cyano, 3-fluoro and 3-chloropyridine, where TMPMgCl·LiCl promoted the C2-H metalation while $TMPMgCl·BF_3·$ LiCl led to the C4-H metalation.[10] Contrary to these regioselectivity patterns, the use of **A** promoted an unprecedentedly regioselective metalation of 3-functionalized pyridines, where metalation occurred selectively at the C6 position despite the classical *ortho* direction imparted by $CONMe_2$, COOEt, COMe and F at the C3 positions (**2Al-o**). This novel metalation protocol also provides a mild and efficient one-pot method for the synthesis of important 2,5-difunctionalized pyridines from readily available 3-substituted pyridines, which previously required several functional group transformation steps from 2,5-disubstituted pyridines. For example, one of the reported preparations of 5-fluoro-2-iodopyridine (**2Ao**) involved substitution of the amino group with iodine following the diazotization of 5-fluoropyridin-2-amine, which was prepared from 5-nitropyridin-2-amine in five steps.[26] Conversely, the metalation of 3-substituted pyridines using **B** occurred selectively at the C2 position (**2Bl-o**), providing a regiodivergent and convenient approach for the synthesis of 2,3-difunctionalized pyridines. Moreover, 3-acetylpyridine was regiodivergently metalated by both **A** and **B** despite the presence of the acidic C-H bonds in the $COCH_3$ moiety. To the best of our knowledge, the C2-H metalation reactions of N, N-dimethyl nicotinamide, ethyl nicotinate and 3-acetylpyridine using various (mixed) metal TMP amides had not been previously reported.

Subsequently, the metalation of 3,5- and 2,6-dihalopyridines (X = Cl and Br) to produce **2Ap-2Bt** was explored using **A** and **B**, as listed in Fig. 2. Notably, the metalations using **A** and **B** exhibited a complementary regioselectivity switch. More specifically, although the reported C4-H metalations of 3,5-dihalopyridines (X = Cl and Br) were limited to lithiation using LDA at -78 ^{o}C;[27] metalation using **A** proceeded at room temperature to cleanly afford the desired products (**2Ap** and **2Aq**). In addition, although the C2-H metalation of 3,5-dibromopyridine was accomplished by TMPMgCl·LiCl,[28] the C2-H selective metalation of 3,5-dichlorpyridine was problematic.[29] Nevertheless, the C2-H metalations of these two compounds occurred smoothly in the presence of **B** at room temperature (**2Bp** and **2Bq**). Furthermore, in the case of 2,6-dihalopyridines (X = Cl and Br), the C4-H and C3-H were efficiently metalated by **A** (**2Ar** and **2As**) and **B** (**2Br** and **2Bs**), respectively. Notably, the direct C3-H metalation of 2,6-dibromopyridine has not been previously documented, and 2,6-dibromopyridin-3-yl zinc iodide was prepared by the direct zincation of 2,6-dibromo-3-iodopyridine (**2Bs**), which was previously synthesized in two steps from 3-aminopyridine or 2,6-dichloropyridine.[30] This regiodivergent metalation can also be well applied to quinoline compound (**3At** and **3Bt**). In this case, the metalation with **A** occurred at C5, similar to that obtained using TMPMgCl·LiCl, whereas the metalation with **B** occurred at C2, similar to that using $TMPMgCl·BF_3·LiCl$.[10]

As outlined in Fig. 2, the metalations of 3-cyanopyridine, 3-bromopyridine, 3-methoxypyridine and 3-isopropoxypyridine occurred exclusively at the C2 position using **A** and **B** (**3u-v**). In contrast, the previously reported metalations of 3-bromopyridine and 3-pyridinol derivatives were mostly limited to C4-H lithiation.[25,31] Further investigations are required to account for the fact that the metalation of these compounds in the presence of **A** did not occur at the C6-H position, as was observed for other compounds (**2Al-o**).

Regiodivergent Pd and Fe-catalyzed deprotonative couplings of pyridines by A. The transition metal-catalyzed coupling reaction involving 2-pyridyl organometallic compounds has always been problematic, as summarized by Willis, et al.[11] Owing to the instability and poor reactivity of 2-pyridylboron reagents, the toxicity of 2-pyridylstannane and the difficulty of removing tin residue, the Pd-catalyzed coupling reactions of 2-pyridylzinc reagents with ArX are commonly employed for the preparation of 2-arylpyridines. Consequently, the pyridyl metal intermediates obtained from C-H lithiation and magnesiation often require transmetalation with a zinc salt prior to the subsequent Negishi coupling reaction. In contrast, our present Pd and Fe-catalyzed C-H couplings of various pyridines promoted by **A** proceeded facilely without transmetalation and required only simple catalytic systems, such as $Pd(dba)_2/PPh_3$ and $FeCl_3$/TMEDA. These practical approaches therefore solve the above cross-coupling issues associated 2-pyridyl metallic compounds. Importantly, these two coupling reactions also demonstrate a unique regioselectivity switch, as presented in Fig. 3.

The Pd-catalyzed arylations listed in Fig. 3 exhibit high functional group tolerance and regioselectivity (**4Ac-o**). A variety of sensitive functional groups such as ketones, esters, cyanides, amides and halogens were well tolerated on both coupling partners. It was also found that the regioselective sites of these Pd-catalyzed couplings were consistent with those of metalation promoted by **A** (**2Ac-n** in Fig. 2). As a result, various 2-aryl-6-functionalized pyridines were conveniently synthesized from readily available 2-functionalized pyridines. For example, 6-arylpicolinate (**4Ac**) and 6-arylpicolinonitrile (**4Ad**) are important precursors for Pyox ligands, and their reported syntheses required three transformations starting from 2-bromopyridine (i.e., Suzuki coupling, N-oxidation and cyanation).[32] In addition, 6-aryl-2-ketopyridines (**4Ae** and **4Af**) are key precursors for pincer ligands and were previously prepared from 2,6-dibromopyrdine in two steps.[33] Furthermore, 6-Aryl-2-halopyridines (**4Ah-j**) are important intermediates for various 2-aryl-6-functionalized pyridines because their halogen substituents can function as versatile handles for further derivatization; and they are often prepared from 2,6-dihalopyrdines.[34] In contrast, the present Pd-catalyzed C-H arylations of pyridines was able to access these highly useful pyridines from 2-functionalized pyridines in a one-pot manner. To the best of our knowledge, the Pd-catalyzed C6-H arylation of the pyridines bearing a classical *ortho*-directing group at the C3 position has not been reported to date.[35] By virtue of the unique regioselectivity of **A** in metalating these pyridines; the current Pd-catalyzed C-H arylation also facilitated the facile preparations of 2-aryl-5-functionalized pyridines from readily available 3-substituted pyridines (**4Al-o**).[36,37]

The Fe-catalyzed couplings of Ar(R)MgX with 2-halopyridine have been reported, however, the corresponding coupling of 2-pyridyl metallics with aryl halides or metal reagents is rare.[11] As outlined in Fig. 3, the Fe-catalyzed oxidative coupling reactions of pyridines mediated by **A** with Ar(R)MgX proceeded smoothly,[38] demonstrating high levels of functional group tolerance and regioselectivity (**4Bc-o**). Various functional groups that are traditionally sensitive to Grignard reagents were well tolerated. Notably, the regioselective sites in Pd-catalyzed couplings were identical to those observed for **A**, however, the regioselective sites in the Fe-catalyzed couplings mediated by **A** were switched, and were identical to those observed for **B**. It was therefore considered that a catalytic amount of the simple Fe catalyst (10 mol% $FeCl_3$/20 mol% TMEDA) in the presence of a stoichiometric amount of **A** frees the metalation sites from interference by **A**; suggesting that metalation promoted by Fe/Ti synergism should occur more easily than that mediated by Ti. Thus, a variety of 2,3-difunctionalized pyridines were synthesized from readily available 2- or 3-functionalized pyridines in a one-pot manner. The prepared 3-arylpicolinic acid derivatives (**4Bc** and **4Bd**) are key precursors for azafluorenones and also building blocks for pharmaceutically active compounds. Their previous preparations involved the Suzuki coupling of uneasily obtained 3-bromo-picolinic acid or the triflate of methyl 3-hydroxypicolinate.[39] Furthermore, 3-aryl-2-halopyridines (**4Bh-j**) are important precursors for antipsychotic agents,[40] aryl 1,2,4-triazolo-[4,3-a]pyridines,[41] and materials science.[42] Compared with their reported syntheses, the present Fe-catalyzed couplings started from 2-halopyridines, and tolerated the halogens that are readily involved in the coupling reactions. Also, this Fe-catalyzed coupling allowed the introduction of an alkyl group at the 2-position (**4Bm** and **5w**).

Regioconvergent couplings of 3-cyanopyridine, 3-bromo-pyridine and 3-methoxypyridine were also achieved at the C2 position by the Pd and Fe-catalyzed couplings (**5u-w** in Fig. 3).

Regiodivergent late-stage diversification of Nicotine and Boscalid. The late-stage diversification of natural products and pharmaceuticals represents a highly efficient and desirable means to produce derivatives for bioactivity and drug discovery studies.[43] With this in mind, the late derivatization of nicotine and boscalid was performed using the developed pyridine metalation, as illustrated in Fig. 4.

Previous regioselective metalations of nicotine have relied on lithiation, which requires the use of specific lithiating reagents and the careful selection of solvents.[44,45] In contrast, metalation using **A** and **B** proceeded smoothly at room temperature in THF and exhibited the desired regiodivergence, providing compounds **6** and **7**, respectively. Additionally, a one-pot Fe-catalyzed direct arylation protocol afforded **8** in a high yield (Fig. 4).

Boscalid is an important fungicide,[46,47] whose Cl-substituted pyridine ring is prone to undergong S_NAr substitutions and transition-metal catalyzed couplings, while its amide group is sensitive to organometallics. Nevertheless, the regiodivergent C-H derivatizations were successfully performed, demonstrating the feasibility of our method for late-stage diversification in complex settings. More specifically, the pyridine ring of boscalid was regioselectively iodinated at C6 or C4 using **A** and **B**, respectively (**9** and **11** in Fig. 4), and obviously, the iodide can be transformed into a range of other functional groups. Furthermore, the Pd and Fe-catalyzed C-H deprotonative couplings promoted by **A** afforded the C6 arylated product **10** and C4 alkylated product **12**, respectively.

Proposed metalation pathway rationalized by DFT calculations. It should be noted that the exact structures of the reagents **A** and **B** remain unclear. Thus, the reaction pathway of **A** with ethyl picolinate was modeled by DFT calculations (Fig. 5), which showed that C6-H metalation of ethyl picolinate may involve magnesiation via intermediate **INT1** and may generate the pyridyl metallic intermediate **INT2**. In addition, DFT calculations clearly indicated that both intermediates were energetically favored. These results agree with the fact that, in most cases, reagent **A** can promote the C6-H metalation of 2- or 3-functionalized pyridines in the present of various *ortho*-directing groups (Figs. 2 and 3). On the other hand, the DFT calculations revealed that the reaction of **B** with ethyl picolinate should involve *ortho* ferration via intermediate **INT3**, wherein the ester acts as an *ortho* directing group through Fe/Ti synergism. In this system, the N and Cl atoms act as bridges (Fig. 5), leading to pyridyl iron intermediate **INT4**. These two intermediates were also found to be energetically favored. This reaction pathway agrees with the fact that reagent **B** can promote the *ortho*-directed metalation and subsequent functionalization of various functionalized pyridines (Fig. 2). Moreover, the reaction sites of Fe-catalyzed coupling reactions of pyridines performed in the presence of reagent **A** (i.e., which are different from those of **A** but identical to those of **B**; Fig. 3) can also be reasonably explained by this *ortho*-ferration promoted by Fe/Ti synergism.[13]

Conclusions

In conclusion, we have developed two novel and practical TMP-based metallic reagents, which could be conveniently obtained by combining TMPMgCl·LiCl with inexpensive and low-toxicity titanate and $FeCl_2$. These two reagents successfully metalated various pyridines at room temperature, demonstrating high functional group tolerance and regioselectivity. Importantly, reagent **A** achieved C6-H metalation beyond the classic *ortho* direction of various 2- and 3-functional groups, whereas reagent **B** promoted regiodivergent C3- or C2-H metalation through *ortho* direction facilitated by Fe/Ti synergism. Due to these outstanding advantages, the problems associated with poor functional group tolerance under mild conditions and limited regiodivergence were effectively addressed, and various previously difficult-to-synthesize pyridine derivatives were easily prepared. Moreover, under the mediation of **A**, the regiodivergent Pd and Fe-catalyzed deprotonative cross couplings of pyridines were facilely achieved using very simple catalysts and without transmetalation, thereby providing a solution to the problem of 2-pyridyl organometallic cross-coupling. Notably, the use of **Ti-1** also renders post-treatment of the present reactions very convenient. These findings are therefore expected to enrich the chemistry of pyridine metalation and TMP bases.

Methods

General procedure for iodization of pyridines by reaction of reagents A with iodine. To a solution of **Ti-1** (956 mg, 3.75 mmol, 0.75 eq) in dry THF (4 mL) was added dropwise a solution of TMPMgCl·LiCl (7.5 mmol, 1.5 eq) in THF though a syringe in 10–15 minutes at 25 ^{o}C under argon atmosphere. The reaction mixture was stirred at 25 ^{o}C for 40 min. In another three-necked flask (50 mL), a pyridine or quinoline compound (5.0 mmol, 1.0 eq) was dissolved in THF (5 mL) under argon atmosphere. To this solution, the reagent A prepared above was slowly added dropwise. After stirred for 40 min at room temperature, the iodine (5.0 mmol, 1.1 eq) was added and the resulting mixture was stirred for 4 h until the reaction was completed (monitored by TLC). The reaction was quenched by adding distilled water (50 mL) under stirring. The resulting solid was filtered and washed by CH_2Cl_2 (50 mL). The filtrate was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and removing the solvent *in vacuum*, the residue was purified by flash column chromatography on silica gel to afford the desired compound.

General procedure for functionalization of pyridines by Pd-catalyzed cross coupling reaction. To a solution of **Ti-1** (956 mg, 3.75 mmol, 0.75 eq) in dry THF (4 mL) was added dropwise a solution of TMPMgCl·LiCl (7.5 mmol, 1.5 eq) in THF though a syringe in 10–15 minutes at 25 ^{o}C under argon atmosphere. The reaction mixture was stirred at 25 ^{o}C for 40 min. In another three-necked flask (50 mL), a pyridine or quinoline compound (5 mmol, 1.0 eq) was dissolved in THF (5 mL) under argon atmosphere. To this solution, the reagent A prepared above was slowly added dropwise. After stirred for 40 min at room temperature, Pd(dba)$_2$ (144 mg, 0.25 mmol, 0.05 eq), PPh$_3$ (131 mg, 0.5 mmol, 0.1 eq) and ArBr (5.0 mmol, 1.0 eq) were added. The resulting mixture was stirred at reflux in a heating mantle for 24 h until the reaction was completed (monitored by TLC). The reaction was quenched by adding distilled water (50 mL) under stirring. The resulting solid was filtered and washed by CH_2Cl_2 (50 mL). The filtrate was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and removing the solvent *in vacuum*, the residue was purified by flash column chromatography on silica gel to afford the desired compound.

Declarations

Data availability

Experimental details, characterization of compounds and copies of NMR data are available with the submitted manuscript. The X-ray crystallographic data for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 2349987 and 2349880. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

X.F.D. conceived and designed the experiments. X.D.M., J.T.L. and M.F.W. performed the experiments. X.F.D. wrote the manuscript. All authors discussed the results and commented on the manuscript.

Competing interests. The authors declare the following competing financial interest(s): A patent has been filed on results of this research.

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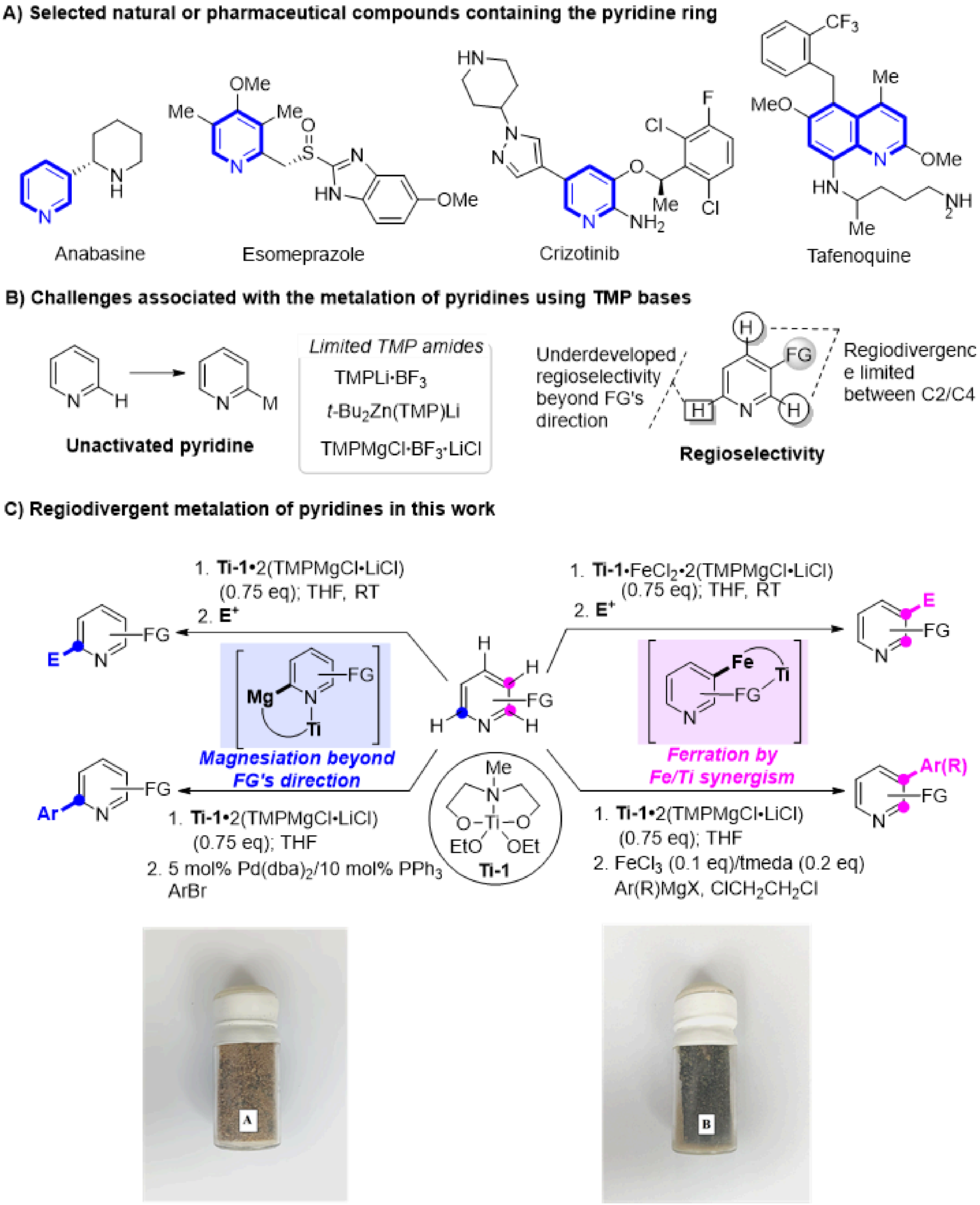
Table

Table 1 is available in the Supplementary Files section.

Figures



Ti-1•2(TMPMgCl•LiCl)

Ti-1•FeCl$_2$•2(TMPMgCl•LiCl)

Figure 1

Comparison of the present study with previous studies. A) Selected natural and pharmaceutical compounds containing the pyridine ring. B) Challenges associated with the metalation of pyridines using TMP bases. C) Regiodivergent metalation of pyridines in this study.

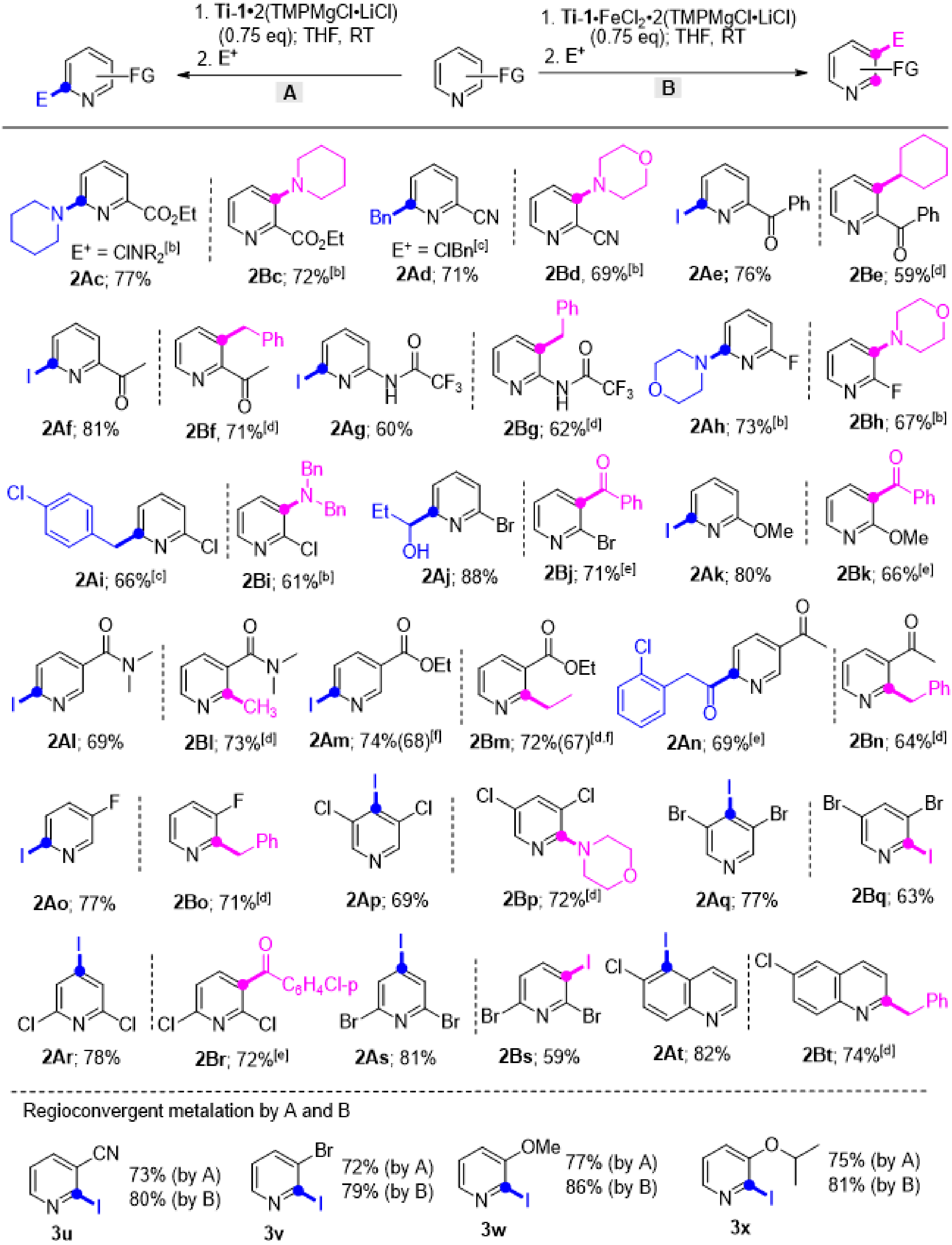


Figure 2

Regiodivergent metalation and functionalization of pyridines using reagents A and B. [a] 5 mmol scale; isolated product yields are given. [b] Reaction with R_2NCl after the addition of CuCN×LiCl. [c] Reaction with BnCl after the addition of CuCN×LiCl. [d] BnCl or RI were used in the reaction. [e] Reaction with RCOCl after the addition of CuCN×LiCl. [f] The yields in parentheses were obtained using solid **A** and **B**.

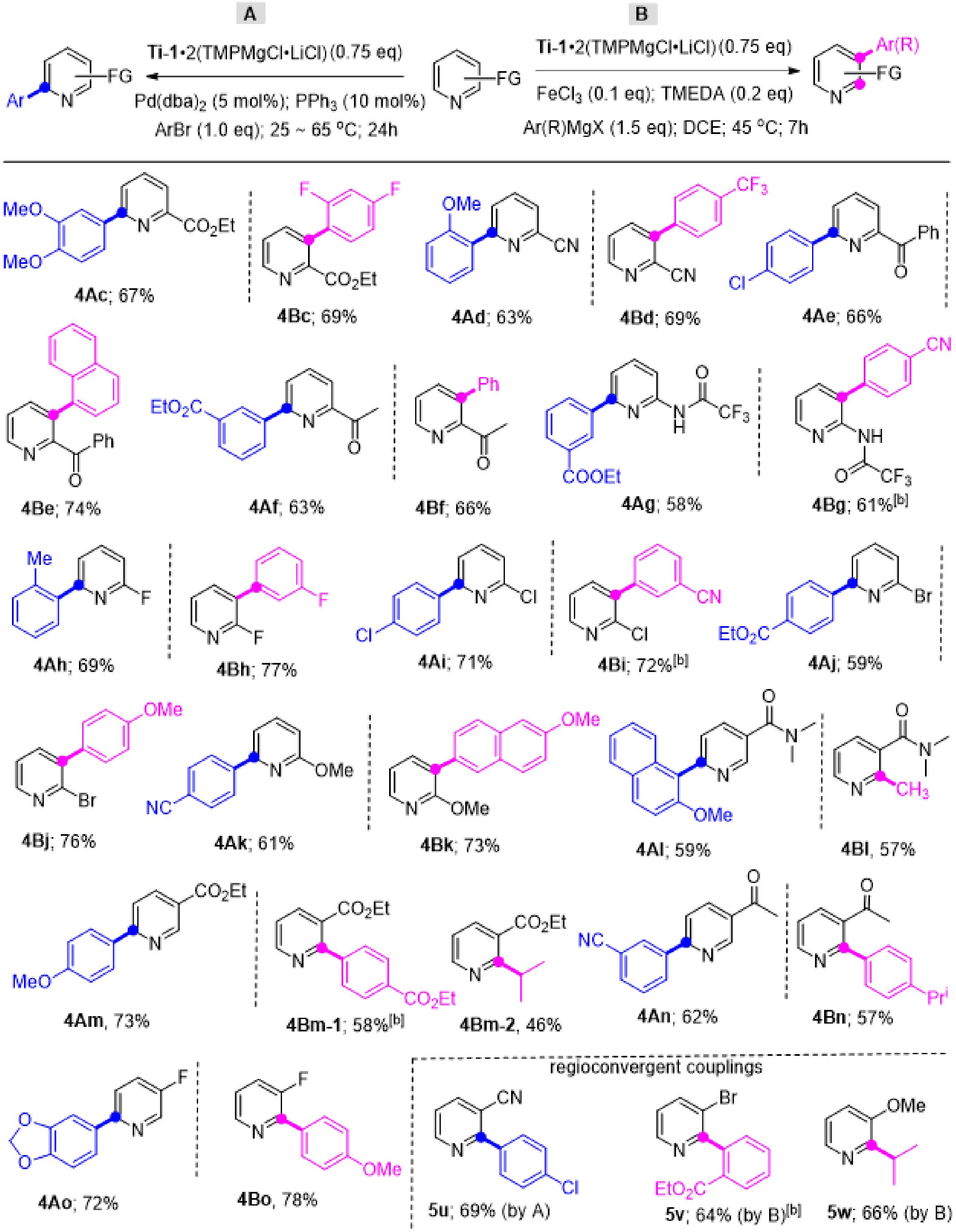


Figure 3

Regiodivergent Pd and Fe-catalyzed deprotonative couplings of pyridines by A. [a] 5 mmol scale; isolated yields are shown; for details see the Supporting Information. [b] The Grignard reagent was prepared using *i*-PrMgCl through Mg/I exchange.

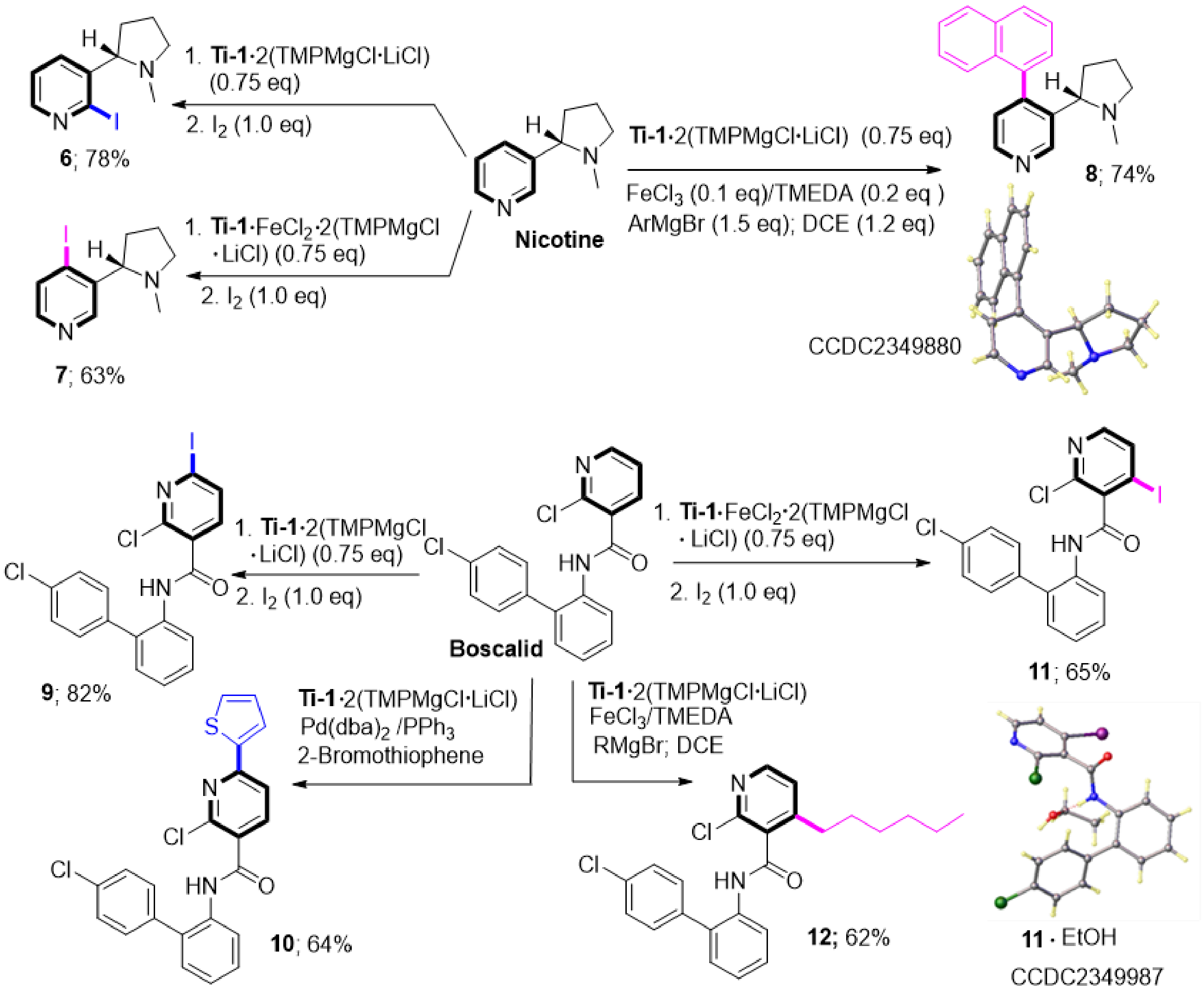


Figure 4

Regiodivergent late-stage diversification of nicotine and boscalid

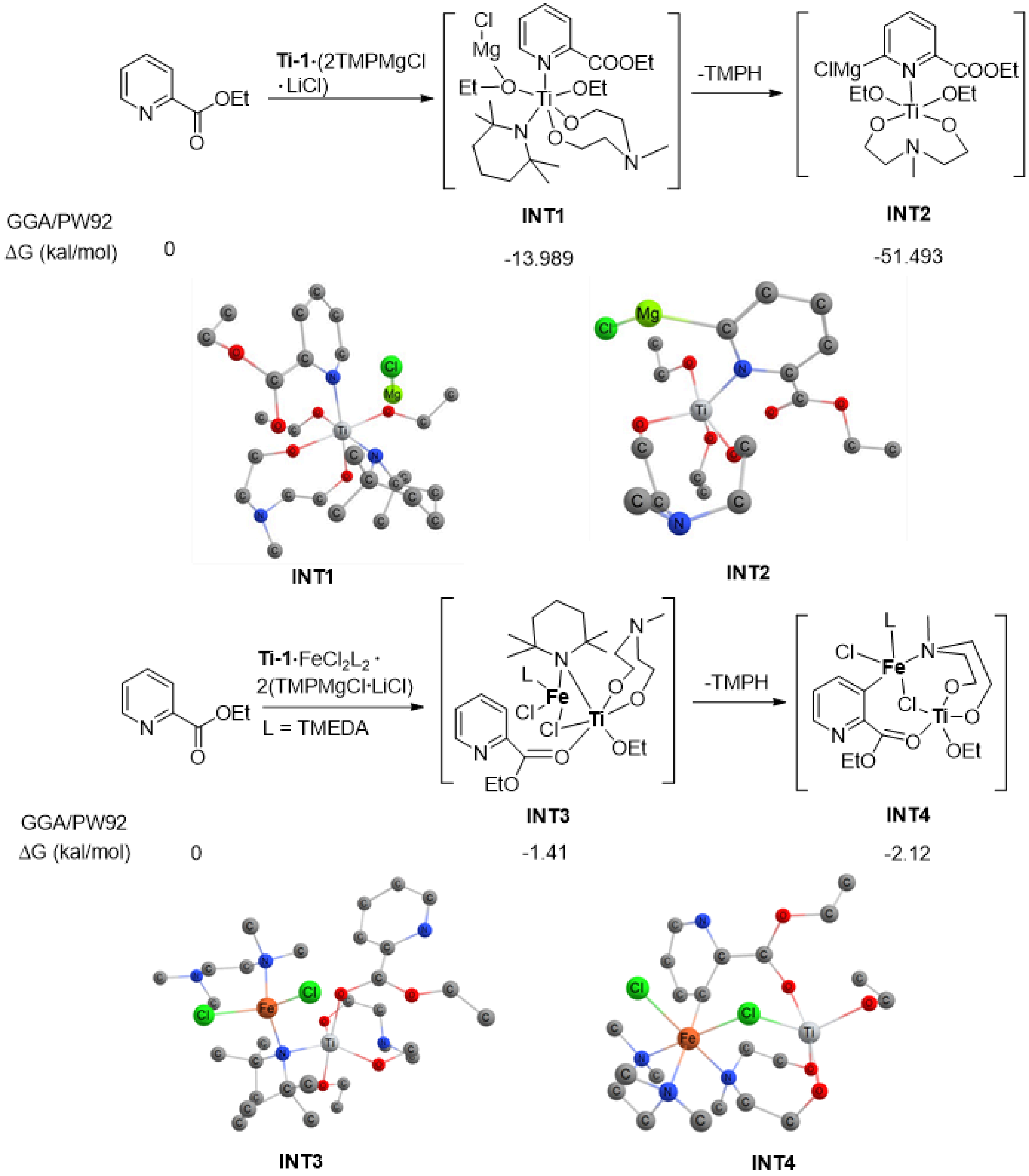


Figure 5

DFT calculations for the regiodivergent metalation of ethyl picolinate

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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