Overcoming the Challenges Towards Selective C(6)-H Alkylation of 2-Pyridone with Maleimide through Mn(I)-Catalyzed C-H bond Activation: Zn assisted Unexpected Migration of Directing group

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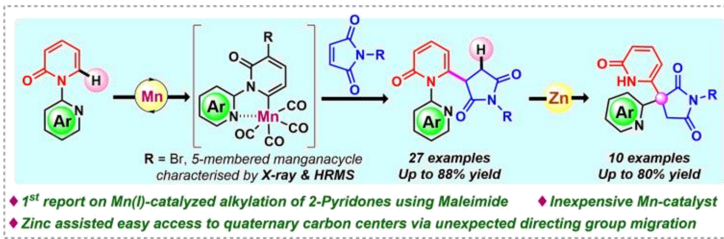


ABSTRACT: An earth-abundant and inexpensive Mn(I)-catalyzed alkylation of 2-pyridone with maleimide has been reported for the first time, in contrast to previously reported Diels-alder product. The directing group was easily removed after functionalization. Notably, unexpected migration of pyridine ring has been discovered in presence of zinc, and acetic acid conditions, which also provides a new route to quaternary carbon centers which contain two heterocycles. Furthermore, single crystal X-ray and HRMS revealed a five-membered manganacycle intermediate. This methodology tolerates a wide variety of functional groups delivering the alkylated products in moderate to excellent yields.

INTRODUCTION

Succinimide derivatives are present in many pharmaceutically active compounds and natural products.[1] The succinimide moiety can be reduced to γ-lactams, pyrrolidines,[2] and it can also be converted into useful functional groups.[3] Substituted succinimide at 3-position is a key structural unit present in many pharmaceuticals and natural products.[4,2b] In this regard, synthesis of succinimide derivatives are considered as one of the valuable organic transformation.

During the last two decades significant progress has been achieved in C–H bond activation reaction leading to the formation of C-C bond by using second and third row transition metal (Rh, Pd, Ir, and Ru) catalysts.[5,6] However, the development of C-H bond activation reactions using first-row transition metals, such as manganese is advantageous on account of its higher abundance in the earth's crust,[7] low cost and low toxicity. So far, only a handful of examples of Mn-catalyzed C–C bond formation via C–H bond activation have been reported.[8]

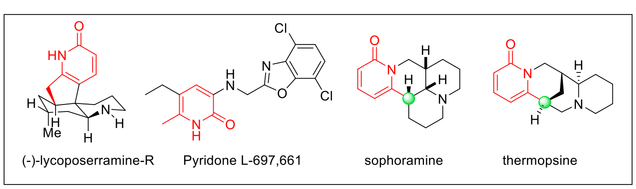
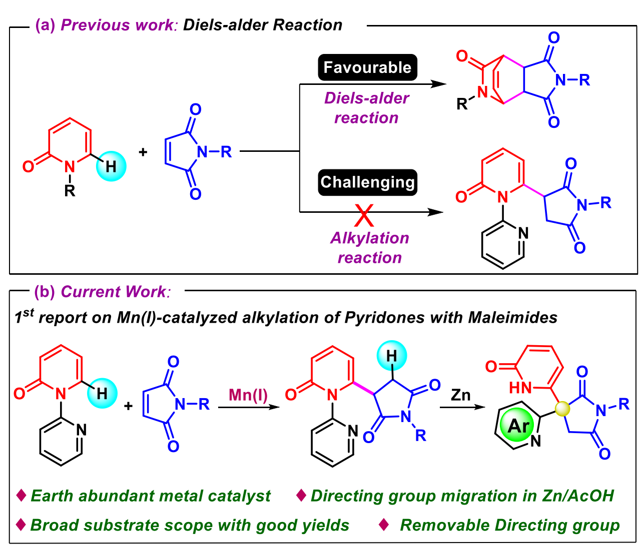


Figure 1. Examples of C-6 alkyl substituted 2-Pyridone core structure in bioactive molecules.

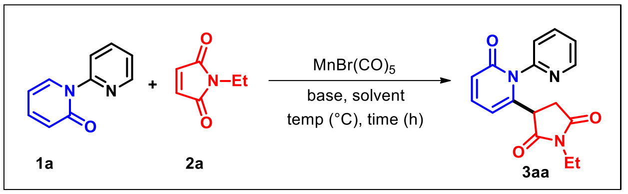
Among all the heterocycles, 2-pyridone is an important heterocycle, which is widely present in numerous biologically active natural products.[9] As compared to C(3)-H,[10] C(4)-H,[11] C(5)-H[12] functionalization of 2-pyridone, selective functionalization at the electron-deficient C(6)-H position of 2-pyridone is a challenging task. Notably, 2-pyridone containing alkyl group at C-6 position is a core structure of many bioactive molecules (Figure 1), therefore alkylation at C-6 position has gained huge attention from the synthetic community in recent years. Though there are few reports on C(6)-alkylation of 2-pyridone,[13] it has been a long-standing challenge for alkylation at the C(6)-position of 2-pyridone derivatives with maleimide as coupling partner by using Mn(I) catalyst. There are some major challenges in alkylation at the selective C(6)-position of 2-pyridones with maleimides such as (i) the reaction of maleimides with 2-pyridones leads to the formation of the

Scheme 1. Comparison with previous works



corresponding Diels-alder products (Scheme 1a).[14] (ii) under basic conditions, succinimide ring undergoes fast hydrolysis.[15] (iii) instead of protodemetalation for the alkylation,[16] facile β-hydride elimination can occur, which results in a Mizoroki–Heck type product.[17] Further, the reaction pathway depend on several factors, like reaction conditions, oxidation states of the metal,[18] and coordination ability of the heteroatom (strong/weak chelation to the metal).[19] Many studies have reported that the β-hydrogens of the alkyl group are not syn-periplanar to the metal, obstructing the β-hydride elimination pathway and resulting in conjugate addition products.[20] Assuming similar conditions will prevail in Mn(I) system, we were curious to check the alkylation of 2-pyridones with maleimides (Scheme 1b). Herein, we have reported the first Mn(I)-catalyzed alkylation at C(6) position of 2-pyridones with maleimide, leading to various biologically active succinimide derivatives.

Table 1. Optimization of Reaction conditions[a]



entry	additive	solvent	temperature	[b]yield of **3aa** (%)
1	Cy_2NH	THF	120 °C	nd
2	Cy_2NH	Toluene	120 °C	nd
3	Cy_2NH	Dioxane	120 °C	nd
4	Cy_2NH	Hexane	120 °C	25
5	Cy_2NH	Acetone	120 °C	34
6	NaOAc	Acetone	120 °C	8
7	Et_3N	Acetone	120 °C	15
8	DIPEA	Acetone	120 °C	18
9[c]	Cy_2NH	Acetone	120 °C	55
10[d]	Cy_2NH	Acetone	120 °C	59
11[e]	**Cy_2NH**	**Acetone**	**120 °C**	**77**
12[f]	Cy_2NH	Acetone	100 °C	54
13[g]	Cy_2NH	Acetone	140 °C	35
14[h]	Cy_2NH	Acetone	120 °C	48
15[i]	Cy_2NH	Acetone	120 °C	69
16[j]	Cy_2NH	Acetone	120 °C	nd
17[k]	-	Acetone	120 °C	trace

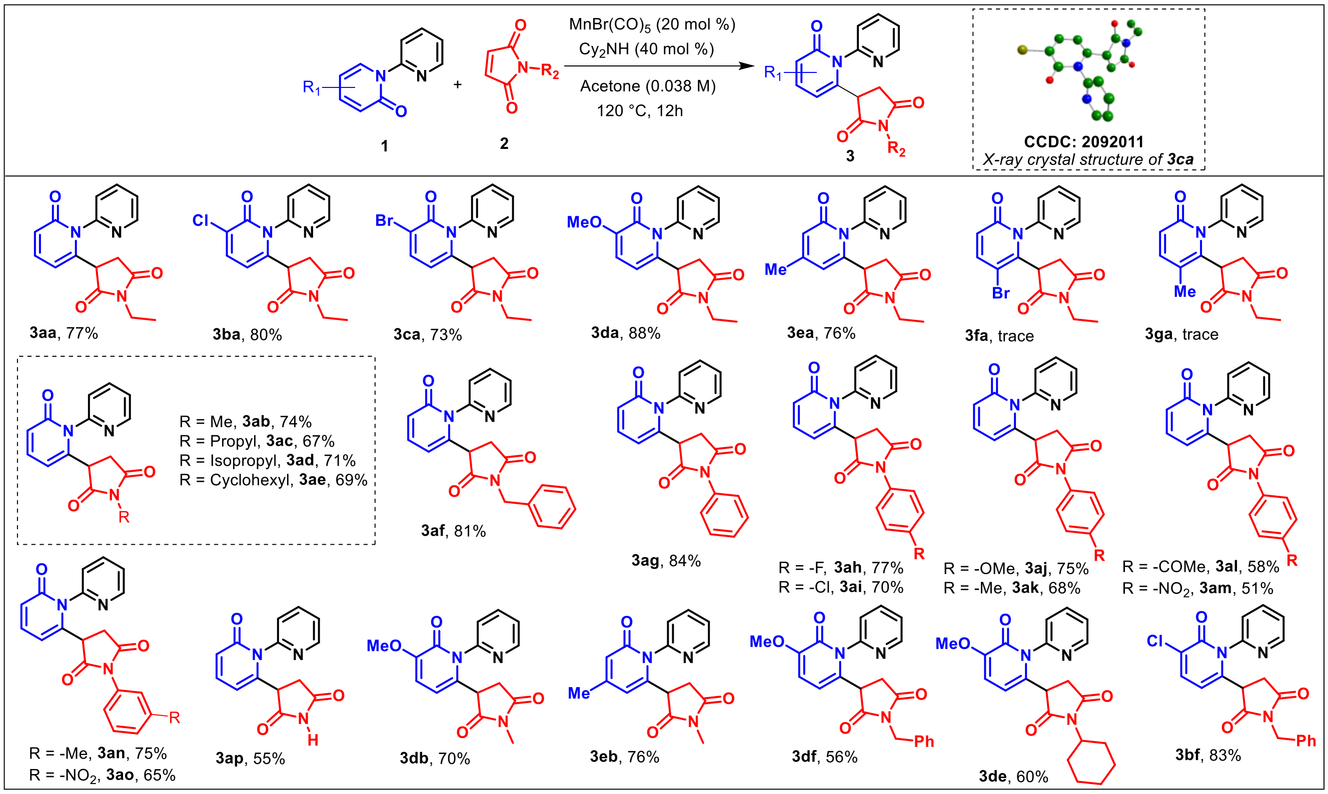
[a]Reaction conditions: **1a** (1 equiv, 0.16 mmol), **2a** (1.2 equiv, 0.19 mmol), [$MnBr(CO)_5$] (10 mol %), Cy_2NH (20 mol %), solvent (0.1 M), at 120 °C for 12 h. [b]isolated yield. [c] solvent (0.038 M). [d]**1a** (0.32 mmol), **2a** (0.16 mmol). [e][$MnBr(CO)_5$] (20 mol %), Cy_2NH (40 mol %). [f]Reaction was carried out at 100 °C. [g]Reaction was carried out at 140 °C. [h]Reaction was carried out for 8 h. [i]Reaction was carried out for 16 h. [j]Reaction without Mn catalyst. [k]Reaction without base. *nd* = not detected.

RESULTS AND DISCUSSION

To get the optimized reaction condition for C-6 alkylation of 2-pyridones, we started the initial study by taking *2H*-[1,2'-bipyridin]-2-ones **1a** as the substrate and maleimide **2a** as the coupling partner with $MnBr(CO)_5$ (10 mol %) as the catalyst, Cy_2NH (20 mol %) as the base in THF at 120 °C for 12 h, but we failed to get any product (Table 1, entry 1). Then, we screened different solvents such as toluene, dioxane, hexane and acetone. To our delight, with hexane and acetone, the desired product was formed in 25% and 34% yields respectively (Table 1, entries 2-5). Enticed from the above results, we continued our optimization by changing different parameters sequentially. By keeping acetone as the solvent, we varied different bases such as NaOAc, Et_3N and diisopropylethylamine (DIPEA) all of them gave inferior results (Table 1, entries 6-8). Interestingly decreasing the solvent concentration improved the yield up to 55% (Table 1, entry 9). In addition, we modified the substrate to coupling partner ratio (2:1) which yielded the corresponding product up to 59% (Table 1, entry 10). Increasing the catalyst (20 mol %) and base (40 mol %) loadings lead to superior result with a 77% yield (Table 1, entry 12) of the desired product. The yield of the product significantly reduced upon lowering or raising the reaction temperature and duration (Table 1, entries 13-16). We conducted two control experiments to understand, the effect of the catalyst and the base. Without the catalyst, the required product was not obtained (Table 1, entry 17), but a trace amount of product was detected in the absence of the base (Table 1, entry 18). These studies confirm that the role of catalyst and base is critical for this reaction.

After getting the optimized reaction conditions for alkylation of 2-pyridones, we explored the scope of different substituted *2H*-[1,2'-bipyridin]-2-ones **1** (Scheme 2) under the same conditions. Neutral *2H*-[1,2'-bipyridin]-2-ones **1a** delivered the desired product **3aa** in 77% yield. Then, we explored the variation of halogen substituent on 3-position of 2-pyridone. Both -Cl, -Br had minimal effect on the yield of the reaction giving 80% and 73% of the alkylated product **3ba**, **3ca** respectively. From the obtained yields it seems 3-Br substrate is slightly more reactive than 3-Cl substrate. The structure of **3ca** was unambiguously confirmed through single crystal X-ray analysis. Next, we examined the effect of electron donating group (3-OMe) at the C3-position which gave 88% yield of product **3da**. Moreover, we have also screened the effect of substituent on C4-position (4-Me) which gave the corresponding alkylated product **3ea** in good yield. Additionally, we also examined the effect of –Br and -Me group at the C5-position. Surprisingly, both the substituents produced trace amount of the products **3fa** and **3ga** respectively. The detrimental effect in the product formation may be due to the steric hindrance near to the reaction site. After exploring the various substrate's scope, we moved on to see the effect of different maleimide derivatives (Scheme 2). Treatment of *2H*-[1,2'-bipyridin]-2-one **1a** with different *N*-alkyl protected maleimides reacted well to furnish 67-74% of the desired product **3ab**-**3ae**. Under similar conditions, *N*-benzyl maleimides gave the corresponding product **3af** in 81% yield. Moreover, different electronically biased *N*-phenyl

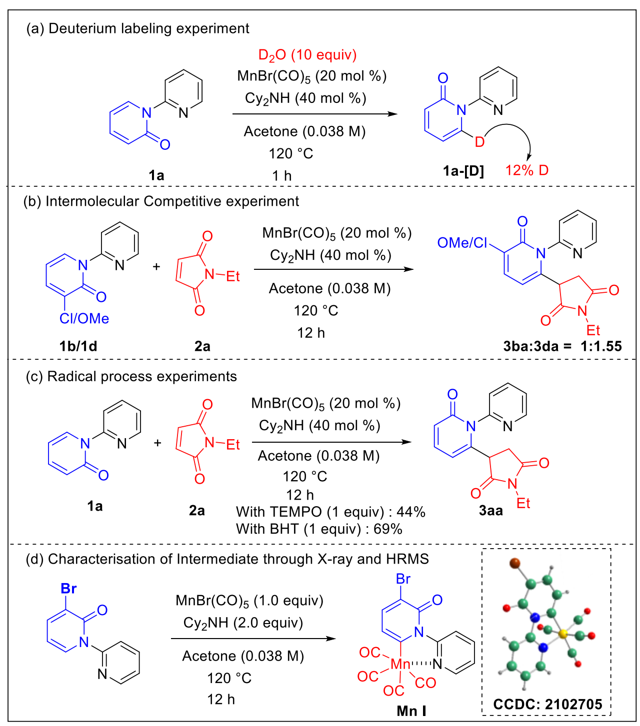
Scheme 2. Scope of *2H*-[1,2'-bipyridin]-2-ones and Maleimides for the Synthesis of alkylated products[a]



[a]Reaction conditions: **1a** (2.0 equiv), **2a** (1.0 equiv), [$MnBr(CO)_5$] (20 mol %), Cy_2NH (40 mol %), Acetone (0.038 M), 120 °C for 12 h.

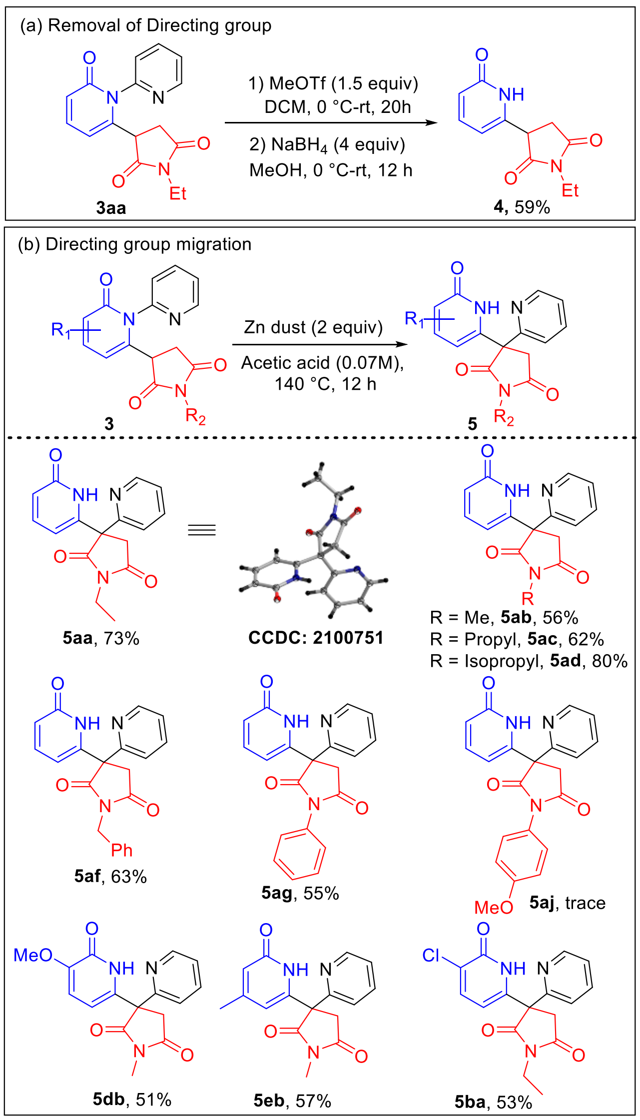
maleimide were also examined. *N*-phenyl maleimide reacted smoothly to gave the product **3ag** in 84% yield. Both fluoro and chloro substituent at the *p*-position of *N*-phenyl maleimide has minimal effect on the yield of the reaction, resulting in 77% and 70% yield of the corresponding product **3ah**, **3ai** respectively. Additionally, we also screened the effect of electron donating and electron withdrawing substituent on phenyl ring of *N*-phenyl maleimide. It was found that electron donating group at the *p*-position (4-OMe, 4-Me) of *N*-phenyl maleimide showed higher reactivity (**3aj**, **3ak)** than electron withdrawing group at the *p*-position (4-COMe, 4-NO_2) of *N*-phenyl maleimides (**3al**, **3am**). Interestingly, substituent at the *m*-position of *N*-phenyl maleimide (*m*-Me, *m*-NO_2) underwent the reaction smoothly giving the product **3an** and **3ao** in 75% and 65% yield respectively. It is worthy to mention that the unprotected maleimide reacted well to give the alkylated product **3ap** in 55% yield. Further, we have explored the scope of the reaction with substitution on both 2-pyridone substrate as well as maleimide substrate. Pleasingly, 3-MeO and 4-Me substrate with *N*-methyl maleimide furnished the desired product **3db** and **3eb** in 70% and 76% yields respectively. In addition to that, 3-MeO pyridone **1d** with *N*-benzyl maleimide **2f** and *N*-cyclohexyl maleimide **2e** were found to be compatible under the standard reaction conditions giving the product **3df** and **3de** in 56% and 60% yield respectively. Also, 3-Cl pyridone **1b** reacted well with *N*-benzyl maleimide **2f** to give desired alkylated product **3bf** with 83% yield. To understand the reaction mechanism, we have done some mechanistic studies (Scheme 3). We performed the reaction with 10 equivalents of D_2O in the absence

Scheme 3. Mechanistic Studies



of maleimide. 2-pyridone was recovered with 12% D incorporation at C(6)-H position (Scheme 3a). It suggests that C-H activation step is reversible under the standard reaction conditions. Intermolecular competition experiment was performed between 3-chloro-*2H*-[1,2'-bipyridin]-2-one **1b** and 3-methoxy-*2H*-[1,2'-bipyridin]-2-one **1d** with maleimide **2a** under standard reaction conditions giving the products **3ba**:**3da** in 1:1.55 ratio (Scheme 3b). This result reveals that electron rich pyridone is more reactive, it provides strong evidence for a BIES reaction.[21] From radical trapping experiment, it was found that on addition of 1 equiv of TEMPO and BHT under standard conditions, displayed 44% and 69% yields (Scheme 3c) respectively.

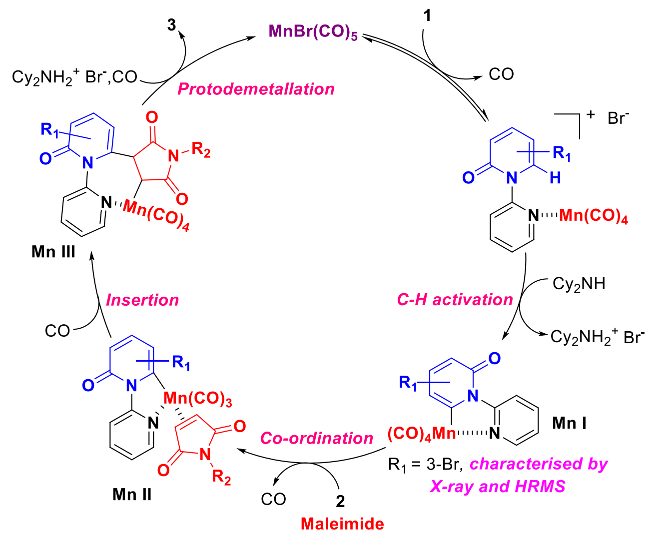
Scheme 4. Synthetic Utility



It reveals that this reaction goes through ionic mechanism. A stoichiometric reaction was performed to isolate the manganacycle, we successfully isolated and characterized the manganacycle intermediate through HRMS and single crystal X-ray studies (Scheme 3d). A demonstrate the application of this methodology in larger scales a 1 mmol scale reaction was performed, we obtained the desired product **3aa** (217 mg) in 73% yield (See supporting information, section **5.3**). Finally, removal of directing group was attempted. Accordingly, treatment of **3aa** with MeOTf followed by $NaBH_4$ gave us 59% yield of **4** (Scheme 4a). Interestingly, when the product **3aa** was treated with Zn/AcOH, we discovered that the directing group migrates leading to C-N bond cleavage followed by the formation of a new C-C bond **5aa** as well as an all carbon quaternary center (Scheme 4b). From single crystal X-ray analysis, we confirmed the structure of **5aa**. It is an interesting molecule with three different *N*-heterocycles with an all carbon quaternary carbon center. Intrigued by its structure, we explored the scope with different alkylated products under the same condition. It was found that alkylated product containing different *N*-alkyl group giving migratory product in good to excellent yield (**5ab**-**5ad**). *N*-benzyl substrate **3af** also gave the desired migrated product **5af** in 63% yield. *N*-phenyl group on succinimide ring underwent reaction smoothly giving **5ag** in 55% yield. 3-OMe group, 4-Me group on pyridone ring also gave migrated product (**5db**, **5eb**) in good yields. Cl group at the 3-position of pyridone gave the corresponding product (**5ba**) in 53% yield. Overall, we have showed an effective way of synthesis of a new class of compounds using our methodology.

Based on mechanistic findings, control experiments and previous literature reports,[8b] we propose a plausible reaction mechanism for the C-H functionalization reaction (Scheme 5). 2-pyridone **1** coordinates to $MnBr(CO)_5$ forming a five membered manganacycle (**Mn I**, characterized through single crystal X-ray and HRMS). Coordination of maleimide with **Mn I** gives **Mn II** intermediate. Subsequently, the maleimide gets inserted into the C-Mn bond of intermediate **Mn II** forming manganacycle **Mn III**. Protodemetallation of **Mn III** intermediate in presence of $Cy_2NH_2^+$ gives the product **3** and regenerates the catalyst.

Scheme 5. Plausible Mechanism



CONCLUSIONS

In conclusion, we have disclosed a Mn(I)-catalyzed C(6)-H alkylation of 2-pyridones with maleimides. The highlight of the methodology is the specific formation of alkylated product rather than the normal formation of the Diels-alder product.

Also, unexpected migration of directing group has been discovered. Which itself is very interesting and leads to unique class of compounds with two important heterocyclic units with a common quaternary center of the succinimide. This methodology was congruent with a wide array of substrates and was also compatible with different functional groups.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via Internet at http://pubs.acs.org.

Optimization studies; Detailed synthetic procedures; Mechanistic studies; characterization data; copies of NMR spectra (^{1}H, ^{13}C, and ^{19}F) of **3aa-3ga**, **3ab-3ap**, **3db**, **3eb**, **3df**, **3de**, **3bf**, **4**, **5aa, 5ab, 5ac, 5ad, 5af, 5ag, 5aj, 5db, 5ba, 5eb** and X-ray crystallography data of **3ca, 5aa** and **Mn I** (PDF File).

FAIR data, including the primary NMR FID files, for compounds **3aa-3ga**, **3ab-3ap**, **3db**, **3eb**, **3df**, **3de**, **3bf**, **4**, **5aa, 5ab, 5ac, 5ad, 5af, 5ag, 5aj, 5db, 5ba, 5eb** (ZIP File).

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Notes

The authors declare no competing financial interest.

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