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Manganese Catalyzed Direct Amidation of Esters with Amines

Zhengqiang Fu, Xinghua Wang, Sheng Tao, Qingqing Bu, Donghui Wei,* and Ning Liu*

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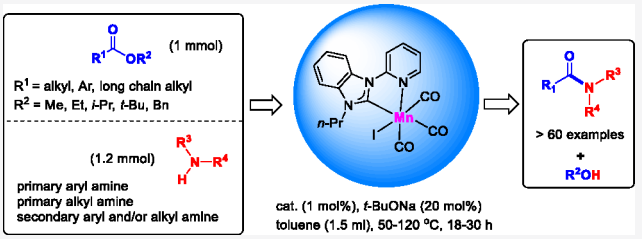
ABSTRACT: The transition metal catalyzed amide bond forming reaction of esters with amines has been developed as an advanced approach for overcoming the shortcomings of traditional methods. The broad scope of substrates in transition metal catalyzed amidations remains a challenge. Here, a manganese(I)-catalyzed method for the direct synthesis of amides from a various number of esters and amines is reported with unprecedented substrate scope using a low catalyst loading. A wide range of aromatic, aliphatic, and heterocyclic esters, even in fatty acid esters, reacted with a diverse range of primary aryl amines, primary alkyl amines, and secondary alkyl amines to form amides. It is noteworthy that this approach provides the first example of the transition metal catalyzed amide bond forming reaction from fatty acid esters and amines. The acid−base mechanism for the manganese(I)-catalyzed direct amidation of esters with amines was elucidated by DFT calculations.



INTRODUCTION

The amide bond is the most fundamental structural motif found in natural products, pharmaceuticals, and biochemistry.[1] Approximately one-quarter of all marketed drugs and two-thirds of all drug candidates contain at least one amide bond in their chemical structure.[2] Conventional methods for the synthesis of amides involve reaction of carboxylic acids with amines under harsh reaction conditions and/or in the presence of stoichiometric amounts of coupling reagents.[3] As a consequence of the ubiquity of amide bonds, a sustainable and atom-economic dehydrogenative coupling method for the synthesis of amides from the coupling of amines with alcohols has been developed,[4] utilizing various transition metal complexes as catalysts such as Mn,[5] Ru,[6] Rh,[7] Os,[8] Fe,[9] and Ag/Al_2O_3,[10] as well as a photocatalysis.[11]

Esters are one of the most fundamental organic molecules, which play a leading role in biologically active molecules, chemical synthesis, and natural products. The direct synthesis of amide from esters and amines is potentially the most useful class of amide bond forming reactions in the synthetic chemistry and pharmaceutical industries.[12] In the last ten years, for the direct amidation of esters with amines, both organocatalyzed[13] and metal-catalyzed[14] approaches have been reported. Although extensively studied, the direct amidation of esters with amines still shows some significant challenges in the area, including broadening the substrate scopes, the use of abundant and commercially available metal catalysts, reducing the use of additives, and decreasing the catalyst loading.[15] In the past decade, several catalyst systems based on the acid−base mechanism have been developed,[16] which have the advantage of proceeding the reaction under mild reaction conditions (Table 1, entries 1−4). In 2005, Porco and co-workers reported a $Zr(OtBu)_4$/HOAt catalytic system, making a nole contribution in the acid−base mechanism[16a] (Table 1, entry 1).

In recent years, the transition metal catalyzed direct amide bond formation from esters and amines has received increasing attentions for its high reactivity and broad substrate scopes. A noble contribution to the transition metal catalysis field for the direct synthesis of amide from esters and amines was recently reported by Garg and co-workers[17] in 2016. They showed that 15 mol % of $Ni(cod)_2$ and 30 mol % SIPr in toluene at 60 °C in the presence of stoichiometric $Al(OtBu)_3$ was sufficient to catalyze the amide bond formation reaction of methyl 1-naphthoate esters with *N*-alkyl aniline derivatives. However, the substrate scopes for the direct amidation remains poor, which limited exploration for more available substrates (Table 1, entry 5). Another contribution to this field was reported by Newman and co-workers[18] in 2017. They employed a palladium complex as catalyst to be able to effectively catalyze the amidation reactions of phenyl esters and aryl amines to form amides. Despite the development is acquired in the aforementioned method, the scope of esters and amines are largely limited to aromatic esters and primary aryl amines (Table 1, entry 6). In the next year, Newman et al.[19] reported an extraordinary work that converted methyl esters and various amines to amides using a $Ni(cod)_2$/IPr catalytic system with a broad range of substrates. However, a few substrates, including second aryl amines, heteroaryl esters and fatty acid esters, are

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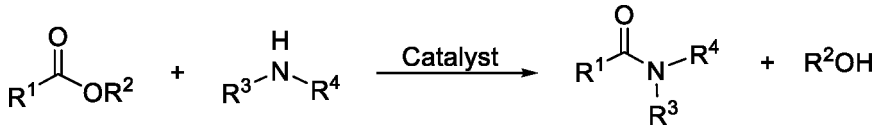
Table 1. Strategies for Amide Bond Formation Using Esters and Aimines



Entry	Catalytic system	R^1				R^2		Amines				Author
		Naph	Ar	Alk	Fatty Acid	Ar	Alk	Alk_I	Alk_{II}	Ar_I	Ar_{II}	
1	$Zr(OtBu)_4$ (10 mol%), HOAt (10 mol%), rt-100 °C, toluene	N/A	Y	Y	N/A	N/A	Y	Y	Y	Y	N/A	Porco[16a]
2	TBD (30 mol%), 75 °C, solvent-free	N/A	Y	Y	N/A	N/A	Y	Y	Y	Y	N/A	Mioskowski[16b]
3	NaOMe (10 mol%) Anhydrous conditions 50 °C, toluene	N/A	Y	Y	N/A	N/A	Y	Y	Y	L	N/A	Mashima[16c]
4	$La(OTf)_3$ (1-5 mol%) rt-70 °C, solvent-free	N/A	Y	Y	N/A	N/A	Y	Y	Y	Y	N/A	Ohshima[16d]
5	$Ni(cod)_2$ (15 mol%), SIPr (30 mol%), $Al(OtBu)_3$ (1.25 equiv), 60 °C, toluene	Y	N/A	N/A	N/A	N/A	Y	N/A	Y	N/A	N/A	Garg[17]
6	Pd(IPr)(allyl)Cl (3 mol%), K_2CO_3 (3 equiv), 110 °C, toluene	Y	Y	Y	N/A	Y	N/A	N/A	N/A	Y	N/A	Newman[18]
7	$Ni(cod)_2$ (10 mol%), Ipr (20 mol%), 140 °C, toluene	Y	Y	Y	N/R	N/A	Y	Y	Y	Y	N/A	Newman[19a]
8	LiHMDS (3 equiv), r.t, toluene	N/A	Y	Y	N/A	Y	N/A	N/A	N/A	Y	N/A	Szostak[20a]
9	LiHMDS (2 equiv), r.t, toluene	N/A	Y	Y	N/A	Y	Y	N/A	Y	Y	N/A	Szostak[20b]
10	Mn-complex (1 mol%), *t*-BuONa (20 mol%), 50-120 °C, toluene	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	This work

[a]**Y** (green) stands for moderate to excellent yields; **N/R** (red) stands for no reaction with experimental evidence; **N/A** (red) stands for experimental data not available; and **L** (blue) stands for low yield of products. Alk_I stands for the primary alkyl amines; Alk_{II} stands for the second alkyl amines; Ar_I stands for the primary aryl amines; and Ar_{II} stands for the second aryl amines.

not feasible for the catalytic system (Table 1, entry 7). Very recently, Szostak and co-workers[20] reported a promising metal-free method under room temperature. Stoichiometric amounts of LiHMDS (2 or 3 equiv) was used in this protocol, and some substrates were not explored (Table 1, entries 8 and 9). Hu and co-workers[21] reported an appealing strategy for reductive amidation of methyl esters and nitroarenes using Ni(glyme)-Cl_2/1,10-phenanthroline as catalysts and using a binary system of Zn powder and chlorotrimethylsilane as a reductant.

In spite of the encouraging progress in this area, there were still some drawbacks existing in these methods: (1) high catalyst loadings and additives were always required; (2) limited substrate scopes. Hence, it is highly desirable to develop a sustainable, powerful strategy for direct amidation to access amide bonds from esters and amines. By the far, the transition metal complexes associated with *N*-heterocyclic carbenes (NHC)-based ligands are the most common catalytic systems for the direct amidation of esters with amines. The transition metal coordination based on hybrid ligands has attracted wide interests in recent years.[22] Hybrid ligands are bidentate or polydentate ligands that contain at least two donors with different coordination abilities.[23] The *trans* effect of hybrid ligands, such as NHC and nitrogen donors, leads to unique properties and robust catalytic performance for the resulting transition metal complexes. Based on our research in the design and synthesis of catalysts,[24] we now report a simple, practical, and convenient synthetic procedure for Mn(I) pincer complexes. The Mn(I) complexes show extremely high activity for the direct amidations from esters and amines with a low catalyst loading (1 mol %). It should be noted that this protocol exhibits an unprecedented wide range of ester and amine scopes and functional group tolerance (Table 1, entry 10).

RESULTS AND DISCUSSION

The pyridine-based pincer-type imidazolium salts **L1-3** were initially prepared according to our reported method.[24c−e] A simple and convenient method was developed for synthesis of Mn(I) complexes. The synthesis was carried out via the reaction of benzimidazolium salts **L1-3** with $MnBr(CO)_5$ under nitrogen atmosphere, as shown in Scheme 1. Mn(I) complexes **1a−c** bearing an iodine anion were prepared via the reactions of ligand **L1** bearing an iodine anion with $MnBr(CO)_5$ in the presence of *t*-BuOK in tetrahydrofuran at 60 °C for 24 h (Scheme 1, top). The Mn(I) complex **1d** bearing a bromide anion was synthesized by employing benzimidazolium salts bearing hexafluorophosphate **L2** (Scheme 1, middle). It is noteworthy that, in the case where 2,6-disubstituted pyridine-bridged benzimidazolium salts **L3** was employed, the carbon atom at the C3 position on the pyridine ring took part in coordination in comparison with coordination of ligands **L1** and **L2** which coordinate with the nitrogen atom bearing pyridine ring, affording the Mn(I) complex **1e** (Scheme 1, bottom). The structures of the Mn complexes **1b**, **1d**, and **1e** were determined by X-ray

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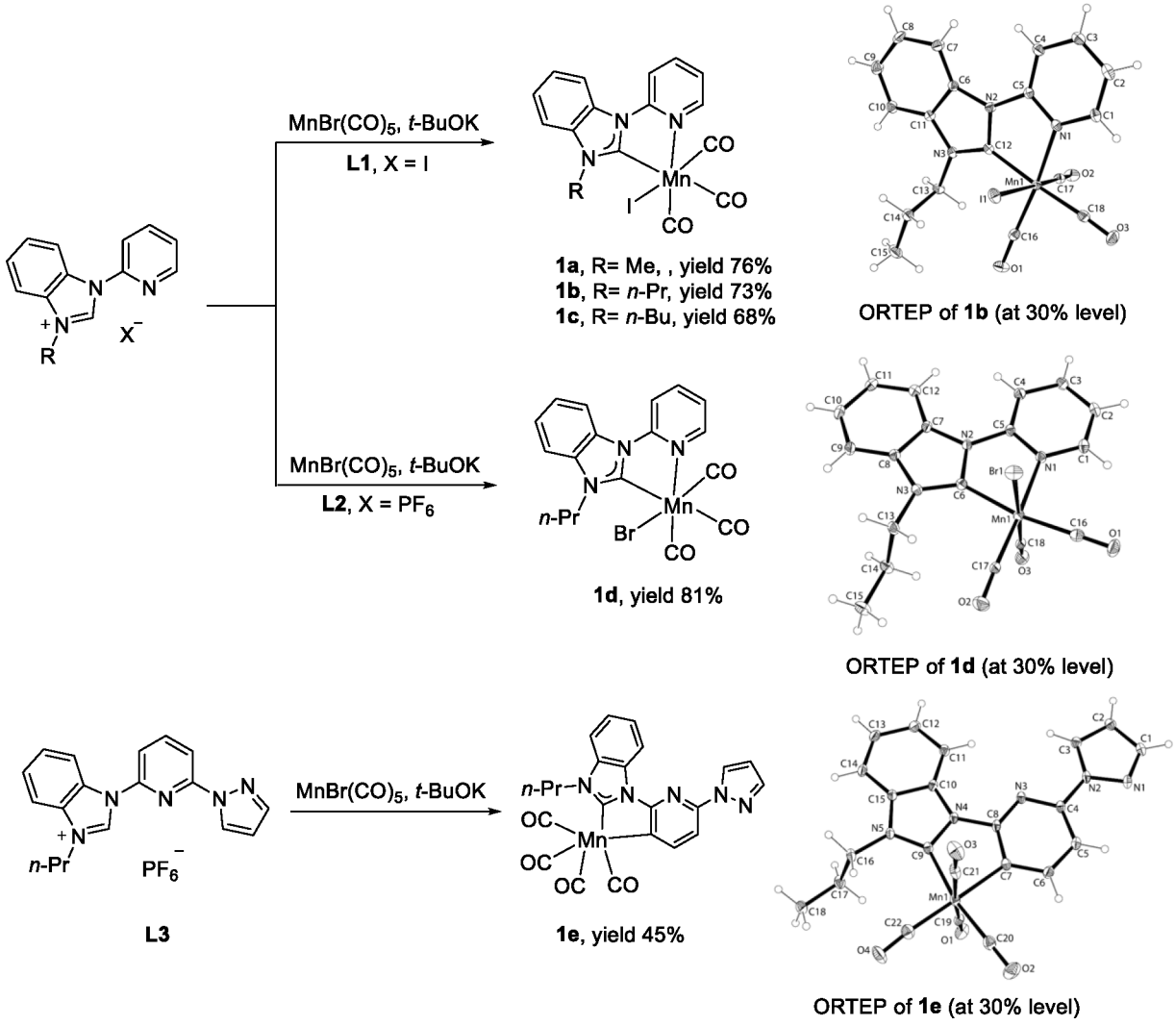
Scheme 1. Manganese Pincer Complexes Used in This Work



crystallography, which confirmed the atom connectivity of **1b**, **1d**, and **1e**, as depicted in Scheme 1. All of the Mn complexes were found to be air and moisture stable, even for 10 days under an air atmosphere.

In initial studies, the reaction of methyl benzoate (**2a**) with 4-methylaniline (**3a**) was used as a benchmark reaction to optimize the reaction conditions (Table 2). To our delight, the reaction proceeded efficiently under nitrogen atmosphere, with the use of an extremely low catalyst loading (1 mol % of Mn complex). Five different coordination mode Mn complexes **1a**−**e** were used as catalysts to investigate the influence of their coordination modes and counteranions on catalytic performance (Table 2, entries 1−5). We were pleased to observe that Mn complexes **1a**−**e** resulted in a moderate to efficient catalytic system for the direct amidation of esters with amines by using toluene as solvent and *t*-BuONa as base under 120 °C (Table 2, entries 1−5).

The influence of coordination modes on the catalytic performance of Mn complexes **1a**-**e** was first explored (Table 2, entries 1−5). Mn complexes **1a**−**d** coordinated with a nitrogen atom bearing pyridine ring showed higher catalytic activity compared with **1e** which coordinated with a carbon atom (Table 2, entries 1−4 vs 5). The most satisfactorily results were obtained using Mn complex **1b** as catalyst (Table 2, entry 2). These results indicated that the coordination modes between Mn and ligands were crucial for the overall reactivity of the Mn complexes. The relatively strong electron-donor ability of nitrogen donor (pyridine ring) compared with carbon donor (benzene ring) is responsible for the results. The strong coordination ability of nitrogen donor is beneficial to stabilize the Mn actvie species in catalytic cycles.

To further understand the influences of the *N*-substituted alkyl in the benzimidazolium salts on the catalytic performance, alkyl chain length of *N*-substituents was explored. The Mn complex **1b** with a moderate length *n*-propyl chain (Table 2, entry 2) showed higher catalytic activity in comparison with a Mn complex **1a** with a shorter methyl chain (Table 2, entry 1) and Mn complex **1c** with a longer *n*-butyl chain (Table 2, entry 3). It is common knowledge that the butyl group has the strongest electron-donor ability compared with the methyl and propyl groups; however, the butyl group has a relatively high steric hindrance. The strong electron-donor for the butyl group is beneficial to stabilize Mn active species in cycle; however, the high steric hindrance prevents the removal of HI to generate new active species. The propyl group possesses good electron-donor ability and moderate size; therefore, the Mn complex **1b** bearing the propyl group showed a relatively high performance.

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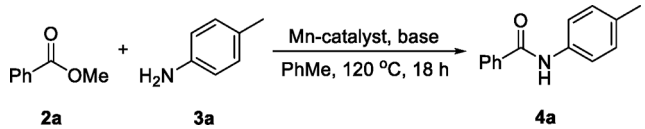
Table 2. Optimization of the Conditions for Direct Amidation[a]



2a **3a** **4a**

entry	cat. (mol %)	solvent	base (mol %)	T (°C)	time (h)	yield (%)
1	**1a** (1.0)	toluene	*t*-BuONa (20)	120	18	46
2	**1b** (1.0)	toluene	*t*-BuONa (20)	120	18	85
3	**1c** (1.0)	toluene	*t*-BuONa (20)	120	18	57
4	**1d** (1.0)	toluene	*t*-BuONa (20)	120	18	49
5	**1e** (1.0)	toluene	*t*-BuONa (20)	120	18	27
6	**1b** (1.0)	toluene	*t*-BuOK (20)	120	18	65
7	**1b** (1.0)	toluene	K_2CO_3 (20)	120	18	16
8	**1b** (1.0)	toluene	Cs_2CO_3 (20)	120	18	20
9	**1b** (1.0)	toluene	K_3PO_4 (20)	120	18	45
10	**1b** (1.0)	toluene	*t*-BuOLi (20)	120	18	51
11	**1b** (1.0)	DMF	*t*-BuONa (20)	120	18	30
12	**1b** (1.0)	CPME	*t*-BuONa (20)	120	18	6
13	**1b** (1.0)	dioxane	*t*-BuONa (20)	120	18	62
14	**1b** (1.0)	MeCN	*t*-BuONa (20)	120	18	53
15	**1b** (1.5)	toluene	*t*-BuONa (20)	120	18	88
16	**1b** (0.8)	toluene	*t*-BuONa (20)	120	18	76
17	**1b** (0.5)	toluene	*t*-BuONa (20)	120	18	56
18	**1b** (1.0)	toluene	*t*-BuONa (50)	120	18	83
19	**1b** (1.0)	toluene	*t*-BuONa (10)	120	18	52
20	**1b** (1.0)	toluene	*t*-BuONa (20)	120	12	63
21	**1b** (1.0)	toluene	*t*-BuONa (20)	120	28	87
22	**1b** (1.0)	toluene	*t*-BuONa (20)	100	18	70
23	**1b** (1.0)	toluene	none	120	18	trace
24	none	toluene	*t*-BuONa (20)	120	18	trace
25	$MnBr(CO)_5$ (1.0)	toluene	*t*-BuONa (20)	120	18	trace
26	$MnCl_2$ (1.0)	toluene	*t*-BuONa (20)	120	18	trace
27	$MnBr_2$ (1.0)	toluene	*t*-BuONa (20)	120	18	trace
28[b]	**1b** (1.0)	toluene	*t*-BuONa (20)	120	18	15

[a]Reaction conditions: methyl benzoate (1 mmol), amine (1.2 mmol), Cat. (1.0 mol %), solvent (1.5 mL), base (20 mol %), 120 °C for 18 h under nitrogen atmosphere in a 25 mL Schlenk tube, and isolated yields. [b]In air.

The influence of the counteranions bearing Mn complexes **1b** and **1d** on the catalytic performance was evaluated (Table 2, entries 2 and 4). As shown in Table 1, the Mn complex **1b** containing an iodine anion (Table 2, entry 2) was much more efficient than the Mn complex **1d** containing a bromide anion (Table 2, entry 4). The leaving ability of the halide anion is in the following order: $I^- > Br^- > Cl^-$. The strong leaving ability of the iodine anion was beneficial to generate Mn active species, so that Mn complex **1b** bearing idoine ainon exhibited high catalytic activity.

Besides *t*-BuONa, others bases including *t*-BuOK, K_2CO_3, Cs_2CO_3, and K_3PO_4 were investigated under similar reaction conditions (Table 2, entries 6−9), and *t*-BuONa was found to be the most effective for the transformation (Table 2, entry 2). We supposed that the low solubility of *t*-BuONa led to the poor result. Therefore, high solubility of *t*-BuOLi was performed (Table 2, entry 10). The results indicated that solubility of bases is not crucial for the performance. It is well-known that *t*-BuOK has the strongest basicity among *t*-BuOLi, *t*-BuONa, and *t*-BuOK, whereas *t*-BuOK has high steric hindrance due to the bulkiness of potassium cation. The stronger basicity for *t*-BuOK is beneficial in removing the hydrogen cation from the amino group; however, the high steric hindrance prevents the hydrogen bond interaction between *t*-BuOK and amines. *t*-BuONa possesses both strong basicity and a moderate size, so that *t*-BuONa has a better deprotonation ability on the amines. The influence of solvent was also explored (Table 2, entries 11−14). When *N*,*N*-dimethylformamide (DMF) and cyclopentylmethyl ether (CPME) were employed, low yields for **4a** were afforded (Table 2, entries 11 and 12). Other solvents, such as 1,4-dioxane and MeCN, showed relatively low performance, affording a moderate yield of **4a** (Table 2, entries 13 and 14). Furthermore, the influences of catalyst loading (Table 2, entries 2 and 15−17) and *t*-BuONa of loading (Table 2, entries 2, 18, and 19) were explored. In view of the cost, a catalyst **1b** loading of 1.0 mol % combined with a *t*-BuONa loading of 20 mol % was appropriate (Table 2, entry 2). The influences of reaction temperature (Table 2, entries 2 and 22) and reaction time (Table 2, entries 2, 20, and 21) were also evaluated, and it was shown that the desired product of **4a** was obtained in improved yield at the temperature of 120 °C, together with a reaction time of 18 h which led to better results (Table 2, entries 2).

Based on the above results, the combined use of Mn catalyst **1b** and *t*-BuONa led to the best performance. However, it is difficult to trigger the reaction by employing the Mn complex **1b** or *t*-BuONa on its own (Table 2, entries 23 and 24). In

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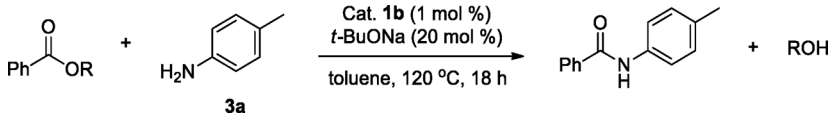
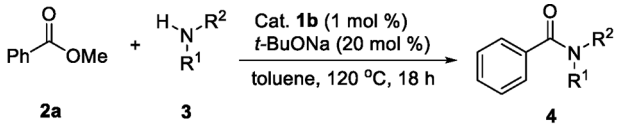
Table 3. Effect of Boiling Point of Alcohol by-Product for Direct Amidation[a]



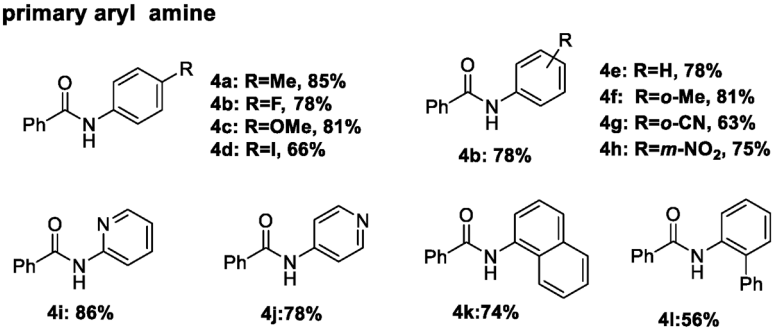
entry	R	additive	yield (%)	bp of ROH (°C)
1	methyl	0	85	65
2	ethyl	0	82	78
3	*n*-pentyl	0	64	136
4	*n*-hexyl	0	41	157
5	methyl	5 equiv MeOH	21	65
6	methyl	10 equiv MeOH	0	65

[a]Reaction conditions: methyl benzoate (1 mmol), amine (1.2 mmol), Cat. **1b** (1.0 mol %), solvent (1.5 mL), base (20 mol %), 120 °C for 18 h under nitrogen atmosphere in a 25 mL Schlenk tube, and isolated yields.

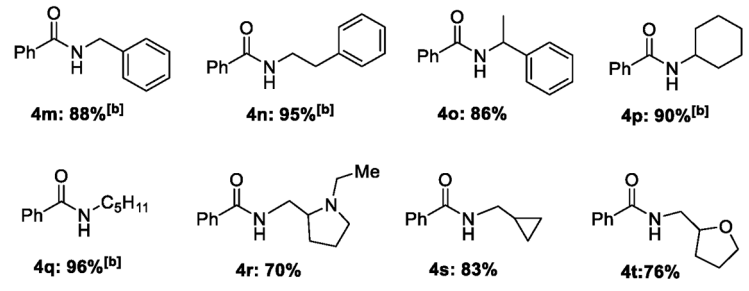
Table 4. Scope of Amines for the Synthesis of Amides[a]



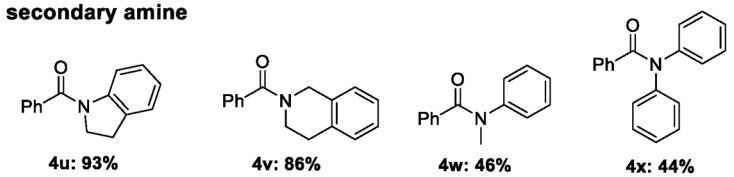
primary aryl amine



primary alkyl amine



secondary amine



[a]Reaction conditions: methyl benzoate (1.0 mmol), amine (1.2 mmol), cat. **1b** (1.0 mol %), toluene (1.5 mL), *t*-BuONa (20 mol %), 120 °C for 18 h under nitrogen atmosphere in a 25 mL Schlenk tube, and isolated yields. [b]90 °C instead of 120 °C.

addition, several common Mn catalysts, such as $MnBr(CO)_5$, $MnBr_2$, and $MnCl_2$, were tested in this reaction, and it was indicated that they were hardly any activity (Table 2, entries 25−27). The results indicated that the pyridine-bridged

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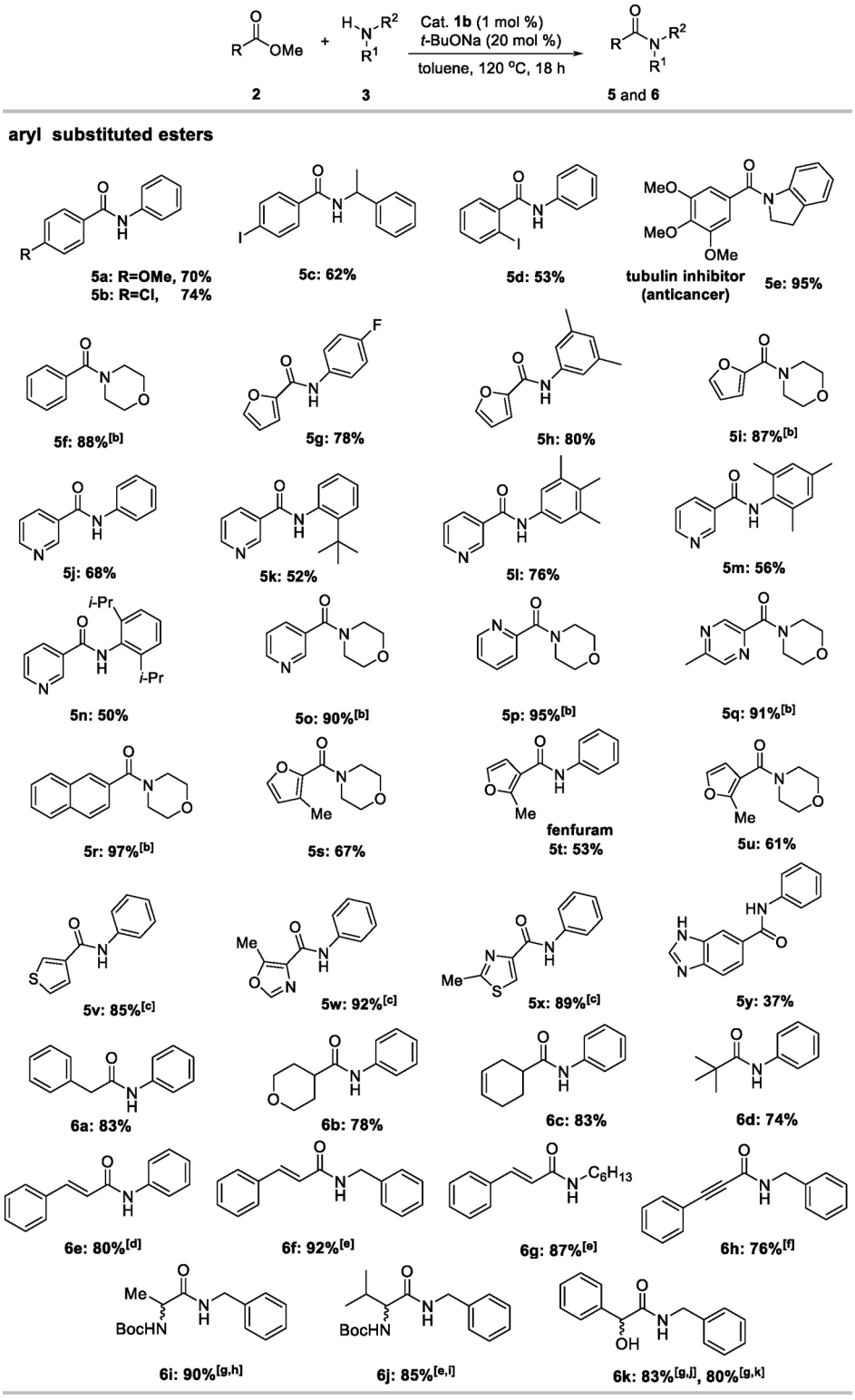
Table 5. Scope of Amines and Esters[a]



[a]Reaction conditions: ester (1.0 mmol), amine (1.2 mmol), cat. **1b** (1.0 mol %), toluene (1.5 mL), *t*-BuONa (20 mol %), 120 °C for 18 h under nitrogen atmosphere in a 25 mL Schlenk tube, and isolated yields. [b]90 °C. [c]Ethyl ester used instead of methyl ester. [d]100 °C. [e]80 °C. [f]50 °C. [g]60 °C. [h]5% ee (ester with 99% ee employed). [i]16% ee (ester with 97% ee employed). [j]1% ee (ester with 99% ee employed). [k]41% ee was obtained with 30 mol % 4-CF_3−C_6H_4−OH as additive.

carbene ligands bearing Mn complexes played an important role in the catalytic activity. Control experiments for the atmosphere suggested that inert atmosphere protection was necessary for a high conversion (Table 2, entries 2 vs 28). It is likely that the oxygen in air significantly inhibits the formation of the active species.

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Next, we used the same substrate as that used in a previously reported catalytic system under the optimized catalytic conditions to compare their catalytic performance, respectively, in Table S3 (see the Supporting Information for details). The Mn-catalytic system showed a competitive catalytic activity compared with other catalytic systems such as Pd(IPr)(allyl)Cl, $Ni(cod)_2$/IPr, $Zr(OtBu)_4$/HOAt, and TBD at high reaction temperature (Table S3, entries 3 vs 4, 5 vs 6, ; 7 vs 8, and 9 vs 10). However, the Mn-catalytic system is not obviously superior among catalytic systems such as $Ni(cod)_2$/SIPr and $La(OTf)_3$ at a low reaction temperature (Table S3, entries 1 vs 2 and 13 vs 14). It is noteworthy that the catalyst loading in the Mn-catalytic system (1 mol %) is much lower than that found in other catalytic systems (3−15 mol %).

The reactions of methyl benzoate with 4-methylaniline will proceed well with the removal of methanol due to its endergonic process. Although no process for methanol removal was used in our experimental procedure, a better product yield was achieved when methanol was achieved as a side product. Therefore, the reason for these results was investigated in Table 3 by employing esters with different ester chain lengths. As shown in Table 3, methyl and ethyl esters proceeded well compared with those esters with longer ester chains such as *n*-pentyl and *n*-hexyl esters. This is probably because the boiling points of the methanol (65 °C) and ethanol (78 °C) generated from methyl and ethyl esters are lower than the reaction temperature (120 °C). Therefore, the methanol and ethanol undergo vaporization to gather in the headspace of the reactor, achieving the effect of removing methanol and ethanol from the reaction system (Table 3, entries 1 and 2). However, the boiling points of pentanol (136 °C) and hexanol (157 °C) are higher than the reaction temperature (120 °C). Thus, pentanol and hexanol are difficult to vaporize (Table 3, entries 3 and 4). While the reactor is closed, the vaporized methanol only gathered in the space above of the reactor, so the headspace of the reactor plays a crucial role in the reaction efficiency. To explore the effect of the reaction headspace, an extra 5 or 10 equiv of methanol was added to the reactor, upon which the yield for the products was found to be significantly diminished (Table 3, entry 5) or inhibited (Table 3, entry 6). In addition, the effect of the different headspace volumes was evaluated, and it was found that the product yield decreased from 85% to 66% when changing volumes from a 25 mL reactor to a 10 mL reactor (see Figure S1 in the Supporting Information for details). These results indicated that the large headspace at the top of the reactor plays a role in removing the methanol byproduct from the reaction system.

To evaluate the scope of the amines, a wide range of amines were investigated in the direct amidation of esters (Table 4). The results suggested that a remarkably broad range of amines are suitable for this Mn-catalyzed system. Both primary aryl amines (Table 4, **4a**−**l**) and primary alkyl amines (Table 4, **4m**−**t**) were smoothly accommodated in this transformation. Of particular note, primary alkyl amines such as benzylamine (Table 4, **4m**), 2-phenylethylamine (Table 4, **4n**), cyclohexanamine (Table 4, **4p**), and amylamine (Table 4, **4q**) showed higher reactivity than the primary aryl amines. The reactions of primary alkyl amines still proceed well even under 90 °C, giving excellent products yields. In addition, the secondary alkyl amines containing *N*-heterocycles (Table 4, **4u** and **4v**) and secondary alkyl/aryl or diaryl amines (Table 4, **4w** and **4x**) were also evaluated in the Mn-catalyzed system. However, *N*,*N*-disubstituted anilines such as *N*-methylaniline (Table 4, **4w**) and diphenylamine (Table 4, **4x**) were found to show moderate reactivity and were converted into the desired products in moderate yields. The reactivity of 4-vinylaniline, 4-ethynylaniline, and *D*-valine were also investigated in our developed Mn-catalyzed system. However, no yields were obtained (please see details in Scheme S2 in the Supporting Information).

To investigate the scope of the reaction, a wide range of ester and amines were evaluated (Table 5). Various esters including aryl (Table 5, **5a**−**f**), furan (Table 5, **5h**−**i** and **5s**−**u**), *N*-heterocyclic (Table 5, **5j**−**q**), naphthyl (Table 5, **5r**), thiophene (Table 5, **5v**), oxazole (Table 5, **5w**), thiazole (Table 5, **5x**), benzimidazole (Table 5, **5y**), and alkyl substituted groups (Table 5, **6a**−**d**) smoothly reacted with primary aryl amines (Table 5, **5a**, **5b**, **5d**, **5g**, **5h**, **5j**−**n**, **5t**, **5v**−**y**, and **6a**−**d**) and secondary alkyls (Table 5, **5e**, **5f**, **5i**, **5o**−**s**, and **5u**), resulting in moderate to excellent yields. We note that **5e** is an important pharmaceutical used as a tubulin inhibitor against cancer, which afforded an excellent yield of 95%. It is noteworthy that sterically hindered *N*-ortho-substituted anilines (Table 5, **5k**, **5m**, and **5n**) are readily tolerated, which led to the production of valuable amides in moderate yields in the Mn-catalyzed system. Heteroaromatic ring-substituted esters were also investigated in Mn-catalyzed system. To our delight, the amidation reaction using ethyl ester with thiophene, thiazole and oxazole substituents took place to deliver the desired amides **5v**−**x** in excellent yields, respectively. The Mn-catalyzed amidation reaction was not limited aromatic ester. Indeed, the aliphatic esters including benzyl (Table 5, **6a**), morpholine (Table 5, **6b**), cyclohexene (Table 5, **6c**) and *tert*-butyl group (Table 5, **6d**) were also available substrates in Mn-catalyzed system. The unsaturated esters such as methyl cinnamate and methyl propiolate were tested in the Mn-catalyzed catalyzed system, the useful functional groups such as double bonds and triple bonds were converted to desired product with high isolated yields (Table 5, **6e**−**h**). In addition, the enantiomerically pure esters at the α position such as alpha-amino acid esters and mandelates were evaluated in our developed Mn-catalyzed system, and high product yields were obtained. The racemization of products was observed under the optimized conditions (Table 5, **6i**−**k**), we inferred that a basic condition lead to α-amino acid derivatives racemization. Ohshima and Mashima[16c] reported that the addition of acidic alcohols such as trifluoromethylphenol effectively inhibited the racemization of the product. As expected, the ee% of product **6k** was up to 41% by the addition of trifluoromethylphenol in our developed catalytic system (Table 5, **6k**).

Given high catalytic efficacy of the Mn-catalyzed amidation, we become interested in describing its mode of reaction. A competition experiment was conducted using aniline as a nucleophile by designing a substrate based on methyl 4-(2-methoxy-2-oxoethyl)benzoate (Table 6). The results indicated that benzylic esters were much more reactive than aryl esters, providing single amidated aliphatic amide **A** and double amidated amide **B** in 66% and 28% yields, respectively. By simply optimization of reaction temperature and the molar ratio of substrates (Table 6, entries 1−4), **A** was obtained as the dominant product with a yield of 76% (Table 6, entry 4).

As shown in Scheme 2, the reactivity bewteen aryl esters and alkyl esters was also evaluated. Methyl benzoate exhibited higher reactivity than that of both methyl tetrahydro-2H-pyran-4-carboxylate and methyl cyclohex-3-ene-1-carboxylate (Scheme 2, eq 1 and 2). Based on the results above, the

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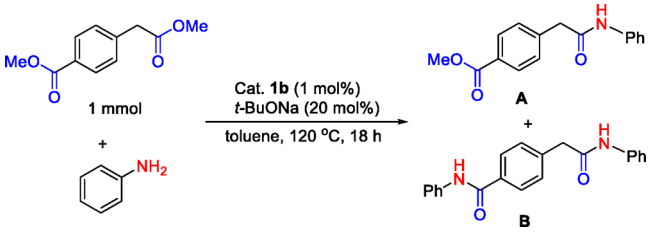
Table 6. Selective Amidation of Different Esters with Aniline[a]



entry	T (°C)	aniline	isolated yield of A (%)	isolated yield of B (%)
1	120	2 equiv	66	28
2	90	2 equiv	70	13
3	60	2 equiv	52	0
4	90	1.2 equiv	76	trace

[a]Reaction conditions: methyl 4-(2-methoxy-2-oxoethyl)benzoate (1.0 mmol), aniline (indicated as Table 6), Cat. (1.0 mol %), solvent (1.5 mL), base (20 mol %), 120 °C for 18 h under nitrogen atmosphere in a 25 mL Schlenk tube, and isolated yields.

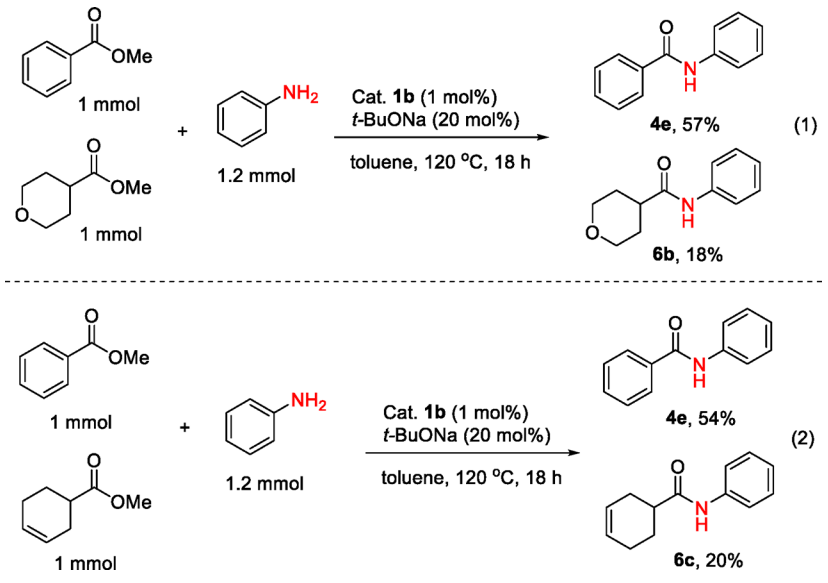
reactivity of esters is in the following order: benzylic esters > aryl esters > alkyl esters (Table 6 and Scheme 2).

Additionally, an intermolecular competitive reactions of aniline and benzylamine with methyl benzoate or aniline and cyclohexanamine with methyl benzoate were explored, respectively, in Scheme 3. The methyl benzoate preferentially reacted with benzylamine rather than aniline to generate the desired product **4m** (Scheme 3, eq 1). This result suggested that benzylamine showed higher reactivity than aniline. In addition, the reactivity difference between aniline and cyclohexylamine was investigated (Scheme 3, eq 2). The result suggested that cyclohexylamine showed higher reactivity than aniline. The reactivity difference between the primary alkyl amines and the secondary alkyl amines was investigated by using methyl benzoate as a reaction partner. The catalytic system showed high selectivity for different amino groups, and direct amidation site-selectively occurred at the primary alkyl amines to give product **C** in 85% yield (Scheme 3, eq 3). Aminoethanols bearing both an aliphatic amine and aliphatic alcohol, which provide two possible reaction routes: the direct amidation of aliphatic amine with methyl benzoate; the transesterification reaction of aliphatic alcohol with methyl benzoate. In our developed Mn-catalyzed system, aliphatic amine of aminoethanol reacted with highly site-selectivity with methyl benzoate to give a hydroxyl amide **D** with highly site-selectivity (Scheme 3, eq 4).

The reaction of benzoic acid or benzamide with aniline was investigated, respectively, in our developed catalytic system. However, the reaction of benzoic acid with aniline did not produce desired product (see details in Scheme S1 in the Supporting Information). The benzamide could react with aniline, giving 10% yield (see details in Scheme S1 in the Supporting Information).

Newman and co-workers[19a] have described that the utility of fatty acid esters as electrophiles for synthesis of plant-oil-based amides remains a challenge. The application for synthesis of amides from biomass is a particularly attractive alternative because it facilitates a shift from the use of fossil resources to renewable resources. Encouraged by the aforementioned promising results, several fatty acid esters and their derivatives were explored in our established protocol (Table 7). We were delighted to find that methyl oleate smoothly amidated with 2-phenylethan-1-amine to give **7a** in a yield of 77%, even at a relatively low reaction temperature (90 °C). Under similar conditions, the desired product of **7a** was obtained in a yield of 75% when ethyl oleate was employed as the electrophiles. Epoxidized methyl oleate was successfully amidated with 2-phenylethan-1-amine and aniline, delivering the products **7b** and **7c** with good yields of 75% and 71%, respectively. Other plant-oil-based fatty acid esters, such as methyl eruclate, methyl linoleate, and especially methyl undecylenate, were found to be compatible with current standard conditions, furnishing the desired plant oil-based products **7d–f** in yields of 81%, 67% and 86%, respectively. To the best of our knowledge, no transition metal catalyzed amidation of fatty acid esters with amines are known, only Ni- or Mn-catalyzed reductive amidation of nitroarenes have been sucessfullly used in the synthesis of amides from fatty acid esters.[21,25]

Scheme 2. Selective Amidation of Different Esters



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Scheme 3. Selective Amidation of Different Amines

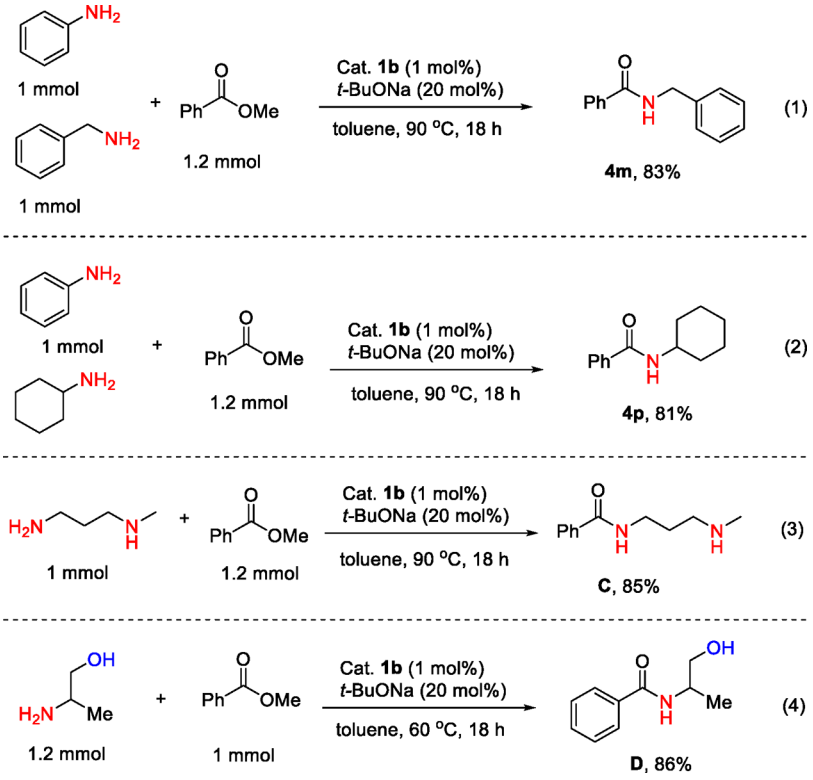
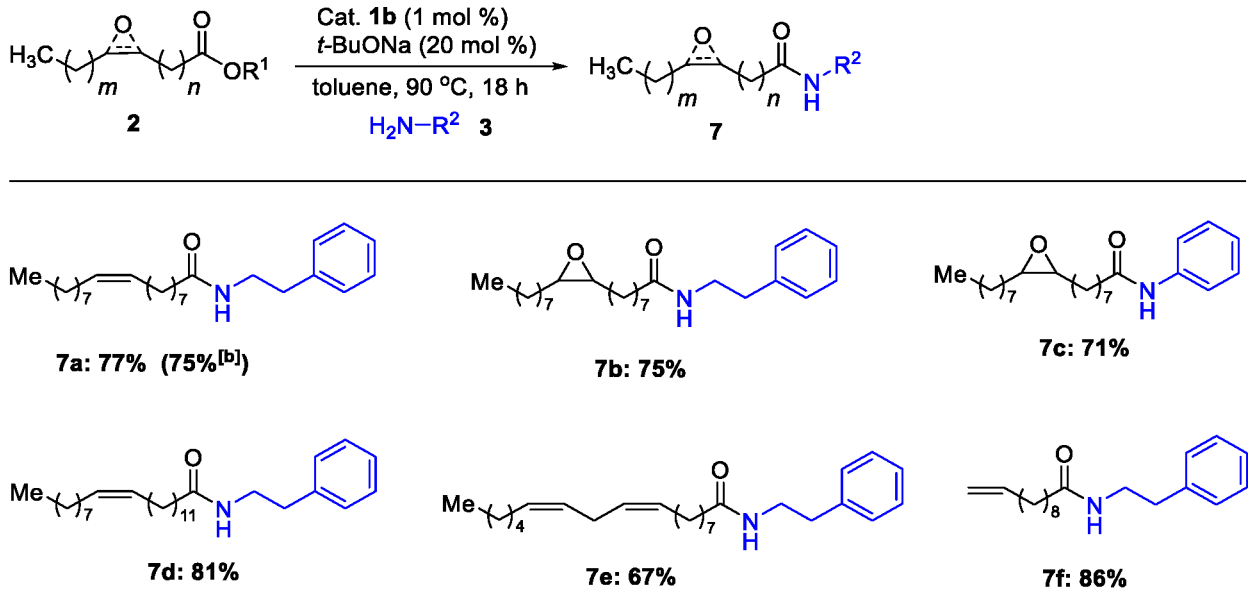


Table 7. Synthesis of Amides from a Fatty Acid Ester[a]



[a]Reaction conditions: fatty acid ester (1.0 mmol), amine (1.2 mmol), cat. **1b** (1.0 mol %), toluene (1.5 mL), *t*-BuONa (20 mol %), 90 °C for 18 h under nitrogen atmosphere in a 25 mL Schlenk tube, and isolated yields. [b]Ethyl ester used instead of methyl ester.

To further demonstrate the compatibility of this protocol, we next proceeded to explore the scope of different ester precursors, since some common esters are not compatible with the reported transition metal-catalyzed systems.[12] As shown in Table 8, various esters, such as ethyl (Table 8, **8a**), benzyl (Table 8, **8d**), aryl (Table 8, **8e**), and sterically hindered *iso*-propyl (Table 8, **8b**) and *tert*-butyl ester (Table 8, **8c**), were found to be suitable electrophiles partners with moderate to high yields for products.

To demonstrate the synthetic application of this Mn-catalyzed amide bond forming approach, the method was applied to the synthesis of substituted amide-containing drugs, such as tigan **E** and itopride **F** (Scheme 4),[26] from benzyl amine and aryl methyl ester. We found that the optimized

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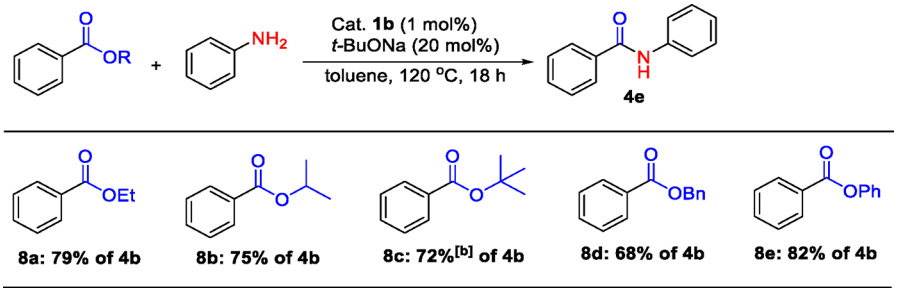
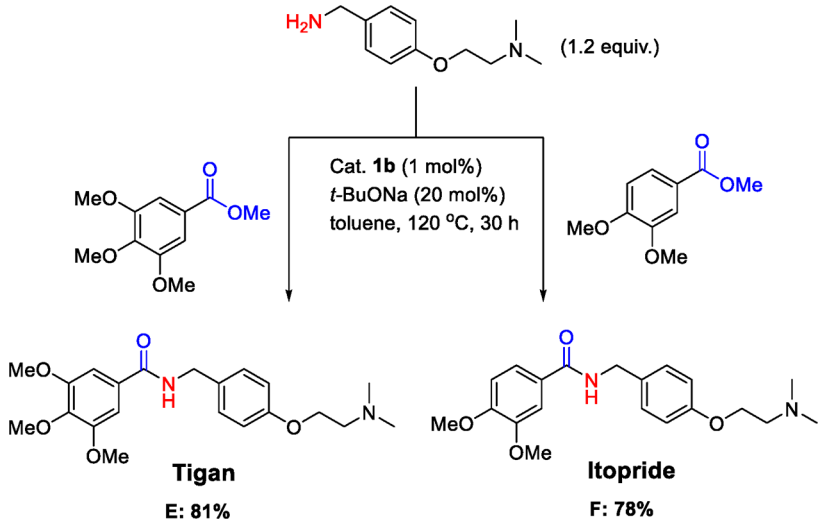
Table 8. Scope of Other Esters[a]

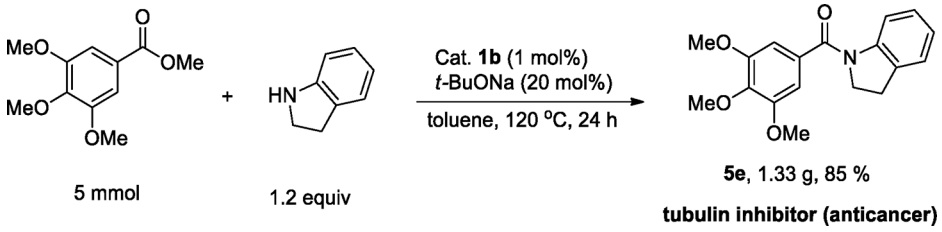


[a]Reaction conditions: ester (1.0 mmol), aniline (1.2 mmol), cat. **1b** (1.0 mol %), toluene (1.5 mL), *t*-BuONa (20 mol %), 120 °C for 18 h under nitrogen atmosphere in a 25 mL Schlenk tube, and isolated yields. [b]140 °C instead of 120 °C.

Scheme 4. Synthetic Application for the Synthesis of Tigan and Itopride



Scheme 5. Gram-Scale Synthesis



reaction conditions are also well-compatible with direct amide bond forming reaction for the synthesis of the two amide-containing drugs **E** and **F**, affording a high yield of 81% and 78%, respectively.

In addition, a gram-scale experiment was carried out under the optimized conditions. The reaction of methyl 3,4,5-trimethoxybenzoate with indoline was easily scaled up to the gram scale to give **5e** with a yield of 85% under the optimized reaction conditions (Scheme 5).

We performed kinetic experiment to determine the order of reaction. Plots of k_{in} versus the concentrations of methyl benzoate and the catalyst gave linear curves (slope = 2.558×10^{-5} M s^{-1}; 1.69×10^{-5} M s^{-1}) indicating a first order rate dependence on methyl benzoate and the catalyst (Figures S15b and S17b in the Supporting Information). Similar kinetic studies by varying the concentration of amine, however, showed no change in k_{in} (Figure S16b in the Supporting Information) suggesting that the reaction is zero order on amine.

DFT calculations were performed to explore the possible mechanisms for the Mn-catalyzed reaction of amine and ester. As shown in Figure 1, two kinds of mechanisms including a oxidative addition-reductive elimination mechanism[17] (red line) and acid−base mechanism[16a,20b] (black line) were considered and investigated at the B3LYP-D3/6-311+G(d, p)/SDD/$SMD_{toluene}$//B3LYP/6-31G(d, p)/SDD/$SMD_{toluene}$ level. For the acid−base mechanism, there are three stages that are involved in the reaction. First, the deprotonation of the primary amine by the *t*-BuO^- ion occurs smoothly via transition state **2-ts** with an energy barrier of 0.2 kcal/mol. Second, the complex of Mn-coordinated with the deprotonated amine (the transition state **4** was supported by IR experiments; see Figure S13 in the Supporting Information for details) nucleophilically attacks the carbonyl carbon of ester for the C−

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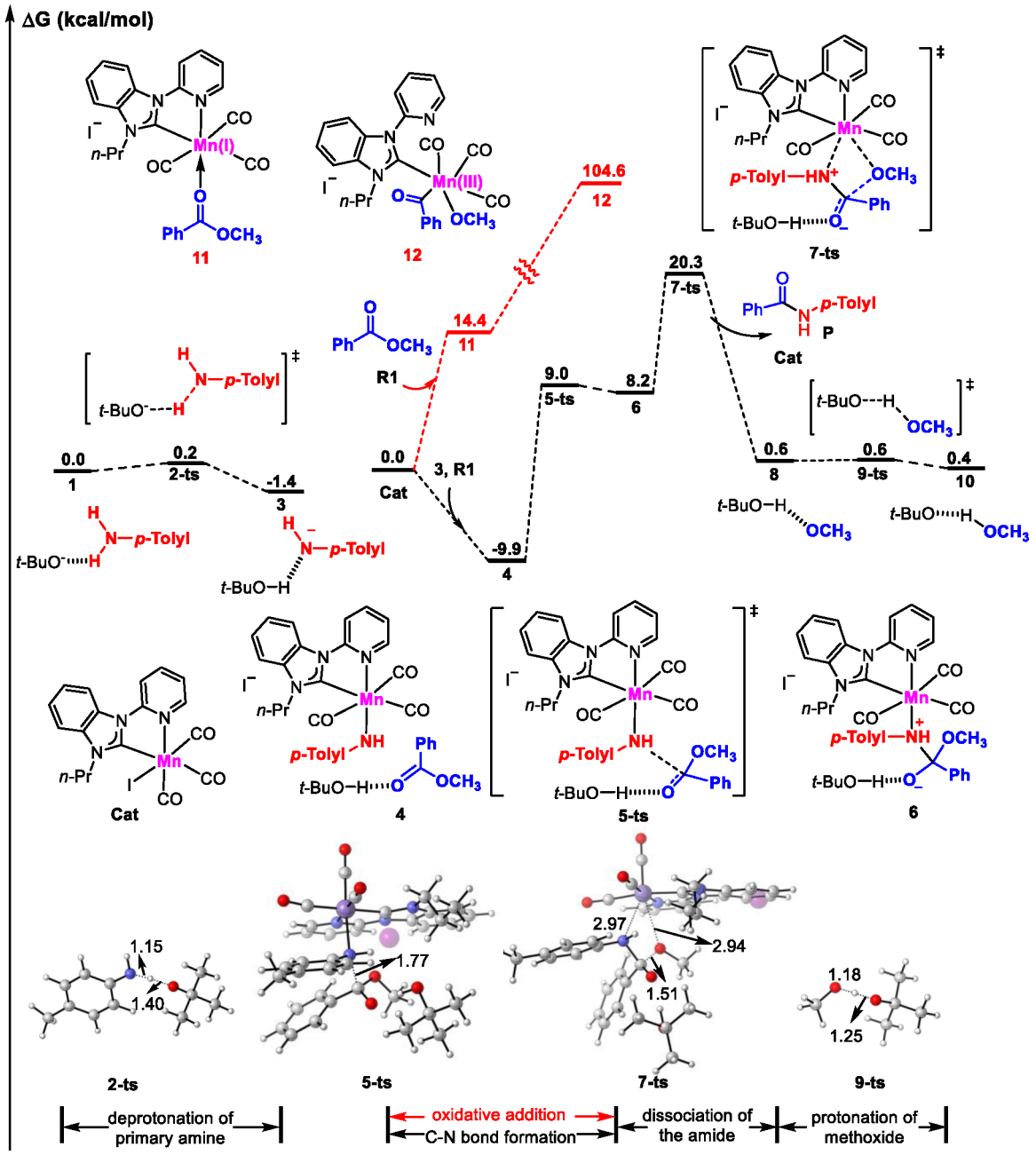

Figure 1. Energy profiles for the oxidative addition-reductive elimination mechanism (red line) and acid−base mechanism (black line) for the Mn-catalyzed reaction (distances in Å).

N bond formation via transition state **5-ts**, which is followed by the dissociation of the amide product via transition state **7-ts**. Third, the CH_3O^- ion is protonated by the in situ generated *t*-BuOH via transition state **9-ts**. The second stage has the highest energy barrier of 30.2 kcal/mol and should be the rate-determining step. For the oxidative addition-reductive elimination mechanism, we have tried but failed to find the transition state via construction of the actual catalyst-mediated reaction model, and the proposed oxidative intermediate **12** has an extremely high energy (104.6 kcal/mol) related to the reactant. Therefore, the calculation results are better rationalized by the acid−base mechanism.

To gain insights into the mechanism, we perfomed theoretical calculations to clarify the reason for the difference in catalytic activity of $MnBr(CO)_5$ and Mn catalyst **1b** by using DFT methods. The results indicated that the energy barrier for $MnBrCO_5$ (41.5 kcal/mol) was higher than that of Mn complex **1b** (30.2 kcal/mol; Figure 2). The energy barriers differences between Mn complex **1b** and $MnBrCO_5$ explained why Mn complex **1b** worked better than $MnBrCO_5$. In addition, the sodium countercation was also included in DFT calculations. As shown in Figure 2, the energy barrier difference between containing sodium ion and noncontaining sodium ion is approximative (Figure 2, 30.2 vs 33.3 kcal/mol), so it will not have an effect for the whole DFT calculation results in Figure 1. The influence of the position of anion in Mn complexes was calculated by removing the iodine anion from **4** and removing the bromide anion from **4″**, respectively (Figure 2). The results indicated that the position of the anion in Mn complexes has no evident effect in the energy barrier

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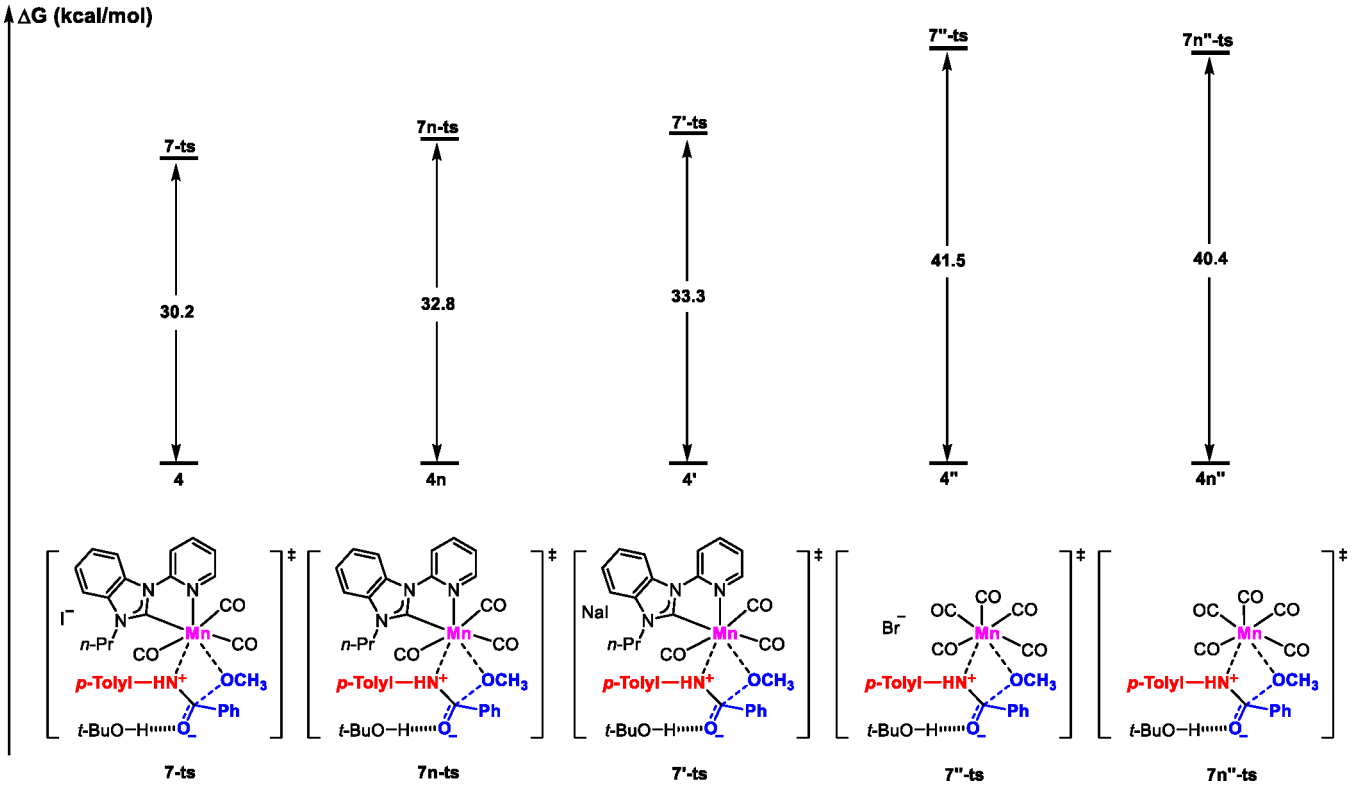

Figure 2. Comparison of energy barriers.

difference (Figure 2, 30.2 vs 32.8 kcal/mol and 41.5 vs 40.4 kcal/mol).

CONCLUSION

In conclusion, we report for first time a manganese-catalyzed amide bond forming reaction with a broad range of esters and amines. The manganese-catalyzed approach exhibits ultra-strong catalytic activity and unprecedented scope for substrates in the field of transition metal catalyzed direct amidation of esters with amines. This catalytic system allows for the use of broad scopes of aromatic, aliphatic, heterocyclic, and fatty acid esters, and various primary aryl amines, primary alkyl amines, as well as secondary alkyl amines, tolerating a diverse range of functional groups and affording a wide range of amides with excellent yields. It is crucial to note that this method provides the first example for the synthesis of plant-oil-based amides from fatty acid esters and amines. The competition experiment for esters indicates that alkyl ester is much more reactive than aryl ester. The competition experiment for amines shows that the reactivity of benzylamine is higher than that of aniline and that the primary alkyl amines show higher reactivity than the secondary alkyl amines. DFT calculations suggest that the manganese(I)-catalyzed direct amidation of esters with amines occurs via an acid−base mechanism rather than an oxidative addition-reductive elimination process. This approach provides more effective and sustainable alternatives for challenging substrates to gain access to amide-containing drugs.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all experimental procedures were performed under an atmosphere of nitrogen using Schlenk techniques. All solvents, esters, amines, and other starting materials were purchased from commercial suppliers and used without further purification.

Preparation of Single Crystals. The crystalline material was prepared via a layer-to-layer diffusion method. The manganese complex **1b** was added into a dichloromethane solution; the manganese complex **1d** was added into a mixture solution of acetonitrile/ethyl ether = 5:1; the manganese complex **1e** was added into the mixture solution of dichloromethane/hexane = 5:1. After 3−5 days, a crystal suitable for single-crystal X-ray diffraction was obtained. Crystallographic data for the structures of the manganese complexes **1b**, **1d**, and **1e** were deposited in the Cambridge Crystallographic Database Centre, supplementary publication Nos. CCDC 1965826, 1965828, and 1961734 for manganese complexes **1b**, **1d**, and **1e**, respectively.

Analytical Methods. The NMR spectra were recorded using a Bruker Avance III HD 400 spectrometer using TMS as the internal standard (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Mass spectroscopy data were collected by using a Shimadzu LCMS-IT-TOF mass spectrometer. The determination of enantiomeric excess was performed by chiral phase HPLC analysis using an Water UPCC instrument and DAICEL CHIRALCEL AD-H column. FT-IR spectra were recorded on Tianjin Gangdong FTIR-650. Single crystal structure determination was conducted using a Bruker D8 Venture X-ray diffractometer equipped with a PHOTON II CPAD detector.

Preparation Procedure for Catalysts 1a−1d. The synthesis of ligands has been reported previously in our works.[24c−e] The manganese complexes were synthesized based on previous literature.[27] A mixture of $MnBr(CO)_5$ (0.5 mmol, 1.0 equiv), ligand (0.6 mmol, 1.2 equiv), and *t*-BuOK (0.5 mmol, 1.0 equiv) was stirred in a 25 mL of Schlenk tube, and the reaction tube was vacuumed and then filled with nitrogen three times under the Schlenk system. Subsequently, THF (2 mL) was added to the reaction tube, and then the mixture was stirred in a heating mantle at 60 °C for 24 h. After cooling to room temperature, THF was removed under reduced pressure using a rotary evaporator. The reaction mixtures were then further washed with acetonitrile (3 × 10 mL) to remove unreacted ligand and $MnBr(CO)_5$, and the crude products were filtered and dried to give the desired product.

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Preparation Procedure for Catalyst 1e. A mixture of $MnBr(CO)_5$ (0.5 mmol, 1.0 equiv), ligand (0.6 mmol, 1.2 equiv), and *t*-BuOK (0.5 mmol, 1.0 equiv) was stirred in a 25 mL Schlenk tube, and the reaction tube was vacuumed and then filled with nitrogen three times under the Schlenk system. Subsequently, THF (2.0 mL) was added to the reaction tube, and then the mixture was stirred in a heating mantle at 60 °C for 24 h. After cooling to room temperature, THF was removed under reduced pressure using a rotary evaporator, and the gray solid product of **1e** was isolated by flash chromatography (petroleum ether (PE)/ethyl acetate (EA) = 5:1).

General Procedure for Amides. Methyl ester (1 mmol), amine (1.2 mmol), Mn catalyst (1.0 mol %), and base (20 mol %) were added to a 25 mL Schlenk tube that was equipped with a magnetic stirrer. The reaction tube was vacuumed and then filled with nitrogen three times under the Schlenk system. Subsequently, toluene (1.5 mL) was added to the reaction tube. The reactor was stirred in a heating mantle at the specified temperature for 18 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the products were isolated by flash chromatography.

Gram-Scale Synthesis. 3,4,5-Trimethoxybenzoate (5 mmol, 1.15 g), indoline (6 mmol), Mn catalyst **1b** (1.0 mol %, 25.2 mg), and *t*-BuONa (20 mol %, 97 mg) were added to a 50 mL Schlenk tube that was equipped with a magnetic stirrer. The reaction tube was vacuumed and then filled with nitrogen three times under the Schlenk system. Subsequently, toluene (4 mL) was added to the reaction tube. The reactor was stirred in a heating mantle at 120 °C for 18 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the products were isolated by flash chromatography to give product **5e** in 85% yield (1.33 g).

Manganese Complexes (1a). **1a** was prepared according to the general procedure. A yellow-orange solid (161.8 mg, 76%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (brs, 1H), 8.49 (d, J = 36.8 Hz, 2H), 8.25 (brs, 1H), 7.94 (brs, 1H), 7.57 (brs, 3H), 4.29 (s, 3H). Mn complex **1a** is paramagnetic, and ^{13}C NMR spectra were not obtained. HRMS (ESI-TOF) m/z: $[M-I]^+$ Calcd for $C_{16}H_{11}MnN_3O_3$ 348.0175; Found 348.0179.

Manganese Complexes (1b). **1b** was prepared according to the general procedure. A yellow-orange solid (163.8 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (brs, 1H), 8.49 (d, J = 34.8 Hz, 2H), 8.25 (brs, 1H), 8.01 (brs, 1H), 7.56 (brs, 3H), 4.70 (s, 2H), 2.07 (brs, 2H), 1.06 (s, 3H). Mn complex **1b** is paramagnetic, and ^{13}C NMR spectra were not obtained. HRMS (ESI-TOF) m/z: $[M-I]^+$ Calcd for $C_{18}H_{15}MnN_3O_3$ 376.0488; Found 376.0496.

Manganese Complexes (1c). **1c** was prepared according to the general procedure. A yellow-orange solid (147.6 mg, 68%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (brs, 1H), 8.49 (d, J = 35.2 Hz, 2H), 8.24 (brs, 1H), 7.98 (brs, 1H), 7.57 (brs, 3H), 4.73 (s, 2H), 2.07 (brs, 2H), 1.50 (brs, 2H), 1.06 (s, 3H). Mn complex **1c** is paramagnetic, and ^{13}C NMR spectra were not obtained. HRMS (ESI-TOF) m/z: $[M-I]^+$ Calcd for $C_{19}H_{17}MnN_3O_3$ 390.0645; Found 390.0656.

Manganese Complexes (1d). **1d** was prepared according to the general procedure. A yellow-orange solid (164.2 mg, 81%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46−7.62 (m, 8H), 4.77 (brs, 2H), 2.08 (brs, 2H), 1.24−1.09 (m, 3H). Mn complex **1d** is paramagnetic, and ^{13}C NMR spectra were not obtained. HRMS (ESI-TOF) m/z: $[M-Br]^+$ Calcd for $C_{18}H_{15}MnN_3O_3$ 376.0488; Found 376.0502. Similar structure to compound **1d** has been reported previously.[27b]

Manganese Complexes (1e). **1e** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a gray solid (84.6 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81−8.79 (m, 2H), 8.27 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.58−7.53 (m, 2H), 6.64 (s, 1H) 4.59 (t, J = 7.6 Hz, 2H), 1.99−1.94 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H). Mn complex **1e** is paramagnetic, and ^{13}C NMR spectra were not obtained. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{17}MnN_5O_4$ 470.0656; Found 470.0652.

N-(p-Tolyl)benzamide (4a).[20b] **4a** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 15:1): a white solid (179.4 mg, 85%), mp = 160.2−162.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (brs, 1H), 7.86−7.84 (m, 2H), 7.55−7.51 (m, 3H), 7.45 (t, J = 7.6 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.9, 135.5, 135.2, 134.3, 131.8, 129.7, 128.8, 127.1, 120.5, 21.0.

N-(4-Fluorophenyl)benzamide (4b).[28] **4b** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (167.8 mg, 78%), mp = 184.6−185.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.31 (s, 1H), 7.97−7.95 (m, 2H), 7.83−7.78 (m, 2H), 7.62−7.52 (m, 3H), 7.20 (t, J = 8.8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 165.9, 158.8 (d, J = 239 Hz), 136.0, 135.3, 132.1, 128.9, 128.1, 122.6 (d, J = 7.8 Hz), 115.6 (d, J = 22 Hz).

N-(p-Methoxyphenyl)benzamide (4c).[19a] **4c** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (183.9 mg, 81%), mp = 156.2−157.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85(d, J = 7.2 Hz, 2H), 7.79(brs, 1H), 7.55−7.52 (m, 3H), 7.47 (t, J = 7.6 Hz, 2H), 6.90 (d, J = 9.2 Hz, 2H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.8, 156.9, 135.2, 131.9, 131.1, 128.9, 127.1, 122.3, 114.4, 55.7.

N-(4-Iodophenyl)benzamide (4d).[29] **4d** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (213.1 mg, 66%), mp = 216.4−217.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 1H), 7.94 (d, J = 7.2 Hz, 2H), 7.70−7.68 (m, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 165.6, 139.0, 137.3, 134.7, 131.7, 128.4, 127.7, 122.4, 87.3.

N-Phenylbenzamide (4e).[18] **4e** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (153.7 mg, 78%), mp = 157.6−158.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (brs, 1H), 7.88−7.85 (m, 2H), 7.65−7.63 (m, 2H), 7.56−7.53 (m, 1H), 7.49−7.45 (m, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.15 (t, J = 7.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.9, 138.1, 135.2, 132.0, 129.3, 129.0, 127.1, 124.7, 120.3.

N-Benzoyl-2-methylaniline (4f).[19a] **4f** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a yellow solid (171.1 mg, 81%), mp = 144.1−144.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89−7.85 (m, 3H), 7.76 (brs, 1H), 7.56−7.52 (m, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.25−7.20 (m, 2H), 7.12−7.08 (m, 1H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.8, 135.9, 135.1, 131.9, 130.7, 129.7, 128.9, 127.2, 126.9, 125.5, 123.5, 17.9.

N-(2-Cyanophenyl)benzamide (4g).[30] **4g** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (139.5 mg, 63%), mp = 157.6−158.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 8.4 Hz, 1H), 8.41 (s, 1H), 7.96−7.93 (m, 2H), 7.68−7.59 (m, 3H), 7.56−7.52 (m, 2H), 7.22 (d, J = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.6, 140.8, 134.5, 133.8, 132.8, 132.3, 129.3, 127.3, 124.4, 121.2, 116.6, 102.2.

N-(3-Nitrophenyl)benzamide (4h).[31] **4h** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (181.5 mg, 75%), mp = 120.0−122.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.11−8.00 (m, 3H), 7.91−7.88 (m, 2H), 7.62−7.58 (m, 1H), 7.55−7.50 (m, 3H),. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.0, 148.8, 139.2, 134.2, 132.6, 130.1, 129.2, 127.2, 126.0, 119.3, 115.0.

N-(Pyridin-2-yl)benzamide (4i).[20b] **4i** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (170.3 mg, 86%), mp = 78.2−78.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 4.0 Hz, 1H), 7.92−7.90 (m, 2H), 7.70 (t, J = 8.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.45−7.40 (m, 2H) 6.98−6.95 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.3, 151.9, 147.7, 138.5, 134.5, 132.1, 128.7, 127.5, 119.8, 114.5.

N-(Pyridin-4-yl)benzamide (4j).[18] **4j** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 1:1): a white solid (154.5 mg, 78%), mp = 202.5−204.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.60 (s, 1H), 8.48 (d, J = 5.6 Hz, 2H), 7.98−7.96 (m, 2H), 7.81−7.79 (m, 2H), 7.63 (t, J = 7.6 Hz,

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1H), 7.55 (t, J = 7.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 166.5, 150.3, 145.9, 134.3, 132.1, 128.5, 127.9, 114.0.

*N-1-Naphthalenyl-benzamide (**4k**).*[19a] **4k** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (183.9 mg, 74%), mp = 162.3−163.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (brs, 1H), 8.00−7.97 (m, 3H), 7.92−7.87 (m, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.61−7.57 (m, 1H), 7.53−7.50 (m, 5H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.4, 134.9, 134.3, 132.5, 132.1, 129.0, 128.9, 127.6, 127.3, 126.5, 126.3, 126.2, 125.9, 121.5, 120.9.

*N-([1,1′-Biphenyl]-2-yl)benzamide (**4l**).*[19a] **4l** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 20:1): a white solid (152.9 mg, 56%), mp = 90.2−91.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J = 8.4 Hz, 1H), 7.93 (s, 1H), 7.50−7.47 (m, 2H), 7.40−7.27 (m, 7H), 7.26−7.22 (m, 2H), 7.19−7.16 (m, 1H), 7.11−7.07 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.0, 138.1, 134.9, 134.8, 132.6, 131.7, 130.0, 129.4, 129.2, 128.7, 128.6, 128.2, 126.8, 124.5, 121.4.

*N-Benzylbenzamide (**4m**).*[19a] **4m** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (185.8 mg, 88%), mp = 104.5−105.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.78−7.75 (m, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.30−7.22 (m, 5H), 6.88 (brs, 1H), 4.56 (d, J = 5.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.6, 138.4, 134.4, 131.5, 128.7, 128.5, 127.8, 127.5, 127.1, 44.0.

*N-Phenethylbenzamide (**4n**).*[19a] **4n** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (213.9 mg, 95%), mp = 116.2−118.0 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 6.8 Hz, 2H), 7.45 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 6.8 Hz, 2H), 7.24−7.20 (m, 3H), 6.50 (brs, 1H), 3.70−3.65 (m, 2H), 2.90 (t, J = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.6, 139.0, 134.7, 131.4, 128.8, 128.7, 128.5, 126.9, 126.6, 41.3, 35.7.

*N-(1-Phenylethyl)benzamide (**4o**).*[19a] **4o** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (193.6 mg, 86%), mp = 91.2−93.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.40−7.32 (m, 6H), 7.28−7.24 (m, 1H), 6.53 (brs, 1H), 5.36−5.29 (m, 1H), 1.58 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.7, 143.3, 134.7, 131.5, 128.8, 128.6, 127.5, 127.1, 126.3, 49.3, 21.8.

*N-Cyclohexylbenzamide (**4p**).*[32] **4p** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (182.8 mg, 90%), mp = 149.2−150.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76−7.73 (m, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 6.23 (brs, 1H), 3.99−3.90 (m, 1H), 2.00−1.97 (m, 2H), 1.75−1.70 (m, 2H), 1.65−1.60 (m, 1H), 1.43−4.32 (m, 2H), 1.27−1.10 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.7, 135.1, 131.2, 128.5, 126.9, 48.8, 33.2, 25.6, 25.0.

*N-Pentylbenzamide (**4q**).*[33] **4q** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a colorless oil (184.0 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.2 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 6.78 (brs, 1H), 3.37 (q, J = 7.2 Hz, 2H), 1.60−1.53 (m, 2H), 1.32−1.24 (m, 4H), 0.86 (t, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.7, 134.8, 131.2, 128.4, 127.0, 40.1, 29.3, 29.2, 22.4, 14.0.

*N-((1-Ethylpyrrolidin-2-yl)methyl)benzamide (**4r**).* **4r** was prepared according to the general procedure. Purification by column chromatography (dichloromethane (DMC)/MeOH = 10:1): a yellow oil (162.5 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 6.8 Hz, 2H), 7.49−7.41 (m, 4H), 3.76−3.71 (m, 1H), 3.47−3.35 (m, 2H), 2.97−2.90 (m, 2H), 2.47−2.36 (m, 2H), 2.01−1.96 (m, 1H), 1.85−1.78 (m, 2H), 1.74−1.70 (m, 1H), 1.19 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.9, 134.3, 131.6, 128.7, 127.2, 63.8, 53.8, 49.2, 40.8, 28.2, 23.3, 13.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{21}N_2O$ 233.1648; Found 233.1654.

*N-(Cyclopropylmethyl)benzamide (**4s**).*[34] **4s** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (145.3 mg, 83%), mp = 75.6−76.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.2 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 6.49 (brs, 1H), 3.28 (t, J = 6.8 Hz, 2H), 1.08−1.00 (m, 1H), 0.54−0.50 (m, 2H), 0.24 (q, J = 4.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.6, 134.8, 131.4, 128.5, 127.0, 45.0, 10.8, 3.6.

*N-((Tetrahydrofuran-2-yl)methyl)benzamide (**4t**).*[19a] **4t** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a brown oil (155.9 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.2 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.44−7.40 (m, 2H), 6.57 (brs, 1H), 4.06 (qd, J = 7.2, 3.6 Hz, 1H), 3.91−3.86 (m, 1H), 3.81−3.74 (m, 2H), 3.33 (ddd, J = 1.24, 7.6, 5.2 Hz, 1H), 2.06−1.98 (m, 1H), 1.95−1.88 (m, 2H), 1.65−1.56 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.7, 134.7, 131.5, 128.6, 127.1, 77.9, 68.3, 43.7, 28.8, 26.0.

*Indolin-1-yl(phenyl)methanone (**4u**).*[20b] **4u** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (207.5 mg, 93%), mp = 125.0−127.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (brs, 1H), 7.56−7.54 (m, 2H), 7.47−7.42 (m, 3H), 7.26−7.20 (m, 2H), 7.02 (brs, 1H), 4.08 (s, 2H), 3.12 (t, J = 8.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.1, 142.7, 137.1, 132.5, 130.4, 128.7, 127.2, 125.0, 124.0, 117.4, 50.9, 28.2.

*(3,4-Dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (**4v**).*[19a] **4v** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a colorless oil (203.9 mg, 86%). ^1H NMR (400 MHz, C_6D_6): δ 7.37−7.34 (m, 2H), 7.16 (s, 1H), 7.08−7.04 (m, 3H), 7.00−6.96 (m, 2H), 6.82 (d, J = 8.0 Hz, 1H), 4.80−4.30 (m, 2H), 3.76−3.12 (m, 2H), 2.35 (brs, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 170.1, 137.2, 134.6, 133.7, 129.7, 129.0, 128.5, 127.7, 127.4, 126.7, 126.6, 49.5, 45.2, 29.4.

*N-Methyl-N-phenylbenzamide (**4w**).*[20b] **4w** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (97.1 mg, 46%), mp = 47.8−48.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 6.8 Hz, 2H), 7.30−7.26 (m, 3H), 7.22−7.17 (m, 3H), 7.10 (d, J = 8.0 Hz, 2H), 3.57 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.6, 144.8, 135.9, 129.5, 129.1, 128.6, 127.7, 126.8, 126.4, 38.3.

*N,N-Diphenylbenzamide (**4x**).*[20b] **4x** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (120.2 mg, 44%), mp = 180.2−182.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 6.8 Hz, 2H), 7.29 (t, J = 8.0 Hz, 5H), 7.23−7.15 (m, 8H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.8, 144.1, 136.2, 130.3, 129.3, 129.2, 128.0, 127.6, 126.5.

*4-Methoxy-N-phenylbenzamide (**5a**).*[20b] **5a** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 15:1): a white solid (158.9 mg, 70%), mp = 177.7−179.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.8 Hz, 2H), 7.76 (brs, 1H), 7.63 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.2 Hz, 2H), 7.14 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 162.6, 138.2, 129.2, 129.0, 127.3, 124.5, 120.3, 114.1, 55.6.

*4-Chloro-N-phenylbenzamide (**5b**).*[16c] **5b** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (171.4 mg, 74%), mp = 194.6−196.2 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 10.32 (brs, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 7.2 Hz, 2H), 7.62−7.60 (m, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 164.5, 139.0, 136.4, 133.7, 129.7, 128.7, 128.5, 123.9, 120.4.

*4-Iodo-N-(1-phenylethyl)benzamide (**5c**).* **5c** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (217.6 mg, 62%), mp = 122.4−123.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.32−7.26 (m, 4H), 7.23−7.19 (m, 1H), 6.27 (s, 1H), 2.27−5.20 (m, 1H), 1.52 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.9, 143.0, 137.9, 134.1,

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128.9, 128.7, 127.7, 126.4, 98.5, 49.5, 21.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{14}INONa$ 374.0012; Found 374.0010.

2-Iodo-N-phenylbenzamide (5d).[35] **5d** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 20:1): a white solid (171.2 mg, 53%), mp = 142.5−144.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.6 Hz, 1H), 7.75 (brs, 1H), 7.61 (d, J = 7.6 Hz, 2H), 7.47−7.44 (m, 1H), 7.36 (q, J = 7.2 Hz, 3H), 7.18−7.09 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.5, 142.1, 140.0, 137.7, 131.5, 129.1, 128.5, 128.3, 124.9, 120.3, 92.6.

Indolin-1-yl(3,4,5-trimethoxyphenyl)methanone (5e).[19b] **5e** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (297.5 mg, 95%), mp = 106.5−107.9 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (brs, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.11 (brs, 1H), 7.02−6.98 (m, 1H), 6.77 (s, 2H), 4.10 (t, J = 7.6 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 6H), 3.11 (t, J = 8.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.6, 153.4, 142.5, 139.8, 132.5, 132.2, 127.3, 125.0, 124.0, 116.7, 104.5, 61.0, 56.3, 50.6, 28.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}NO_4$ 314.1387; Found 314.1388.

4-Benzoylmorpholine (5f).[19a] **5f** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (168.2 mg, 88%), mp = 71.5−72.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.39 (m, 5H), 3.73−3.45 (m, 8H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.3, 135.3, 129.8, 128.5, 127.0, 66.8, 48.2, 42.5.

N-(4-Fluorophenyl)furan-2-carboxamide (5g).[25] **5g** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): an off-white solid (160.1 mg, 78%), mp = 103.1−105.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.63−7.58 (m, 2H), 7.47−7.46 (m, 1H), 7.20 (qd, J = 3.6, 0.8 Hz, 1H), 7.05−7.00 (m, 2H), 6.52 (q, J = 1.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.5 (d, J = 242 Hz), 156.2, 147.6, 144.3, 133.4 (d, J = 2.8 Hz), 121.8 (d, J = 7.9 Hz), 115.7 (d, J = 28 Hz), 115.3, 112.6.

N-(3,5-Dimethylphenyl)furan-2-carboxamide (5h).[36] **5h** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (172.1 mg, 80%), mp = 88.6−89.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (brs, 1H), 7.47−7.46 (m, 1H), 7.30 (s, 2H), 7.21−7.20 (m, 1H), 6.78 (s, 1H), 6.52 (q, J = 1.6 Hz, 1H), 2.30 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.1, 148.0, 144.2, 138.8, 137.3, 126.3, 117.8, 115.1, 112.6, 21.4.

Furan-2-yl(morpholino)methanone (5i).[19a] **5i** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a yellow oil (157.5 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, J = 2.0, 0.8 Hz, 1H), 7.01 (dd, J = 3.2, 0.8 Hz, 1H), 6.47 (dd, J = 3.6, 2.0 Hz, 1H), 3.79 (brs, 4H), 3.73−3.71 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.2, 147.8, 143.9, 116.9, 111.5, 67.0, 46.8.

N-Phenylnicotinamide (5j).[18] **5j** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (134.7 mg, 68%), mp = 119.2−120.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.02−8.94 (m, 2H), 8.63 (t, J = 4.4 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.32−7.27 (m, 3H), 7.15−7.11 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 152.1, 148.1, 137.7, 135.6, 131.0, 129.1, 125.1, 123.6, 120.9.

N-(2-Isopropylphenyl)nicotinamide (5k).[19b] **5k** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (132.2 mg, 52%), mp = 179.2−180.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.13 (s, 1H), 8.78 (s, 1H), 8.24 (d, J = 7.2 Hz, 1H), 8.03 (s, 1H), 7.64 (s, 1H), 7.47−7.43 (m, 2H), 7.30−7.21 (m, 2H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.1, 152.7, 147.9, 143.4, 135.5, 134.8, 130.7, 128.4, 127.1, 127.0, 126.9, 123.9, 34.8, 30.9.

N-(3,4,5-Trimethylphenyl)nicotinamide (5l). **5l** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (182.5 mg, 76%), mp = 174.6−175.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.05 (s, 1H), 8.66 (d, J = 4.8 Hz, 1H), 8.48 (brs, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.35−7.32 (m, 1H), 7.26−7.25 (m, 2H), 2.23 (s, 6H), 2.12 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.0, 152.2, 148.1, 137.2, 135.5, 134.6, 132.1, 131.0, 123.6, 120.1, 20.7, 15.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2O$ 241.1335; Found 241.1347.

N-Mesitylnicotinamide (5m).[19b] **5m** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (134.5 mg, 56%), mp = 177.2−178.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.21 (s, 1H), 8.06−8.03 (m, 1H), 7.24−7.19 (m, 1H), 6.77 (s, 2H), 2.18 (s, 3H), 2.04 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.5, 152.1, 148.3, 137.2, 135.5, 135.3, 131.0, 130.4, 129.0, 123.6, 21.0, 18.2.

N-(2,6-Diisopropylphenyl)nicotinamide (5n).[19b] **5n** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (141.1 mg, 50%), mp = 230.7−232.7 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.09 (s, 1H), 8.71 (d, J = 3.2 Hz, 1H), 8.18 (dt, J = 8.0, 2.0 Hz, 1H), 7.93 (s, 1H), 7.37−7.32 (m, 2H), 7.23 (s, 1H), 7.21 (s, 1H), 3.10 (hept, J = 7.2 Hz, 2H), 1.18 (d, J = 6.8 Hz, 12H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3, 152.5, 148.1, 146.5, 135.7, 131.0, 130.4, 128.8, 123.8, 123.7, 29.0, 23.7.

Morpholino(pyridin-3-yl)methanone (5o).[19a] **5o** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 2:1): a yellow liquid (172.9 mg, 90%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.65−8.63 (m, 2H), 7.73 (dt, J = 8.0, 2.4 Hz, 1H), 7.34 (dddd, J = 8.0, 4.8, 0.8 Hz, 1H), 3.74−3.43 (m, 8H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.8, 151.0, 148.0, 135.1, 131.2, 123.6, 66.8, 48.2, 42.7.

Morpholino(pyridin-2-yl)methanone (5p).[37] **5p** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 2:1): a colorless liquid (182.5 mg, 95%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, J = 4.8 Hz, 1H), 7.82 (dt, J = 7.6, 2.8 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.38−7.33 (m, 1H), 3.81 (s, 4H), 3.69−3.67 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.4, 153.6, 148.2, 137.2, 124.6, 124.1, 67.0, 66.8, 47.7, 42.7.

(5-Methylyrazin-2-yl)(morpholino)methanone (5q).[19a] **5q** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 2:1): a yellow liquid (188.5 mg, 91%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.33 (s, 1H), 3.74 (s, 4H), 3.63 (s, 4H), 2.55 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 155.1, 145.8, 144.9, 142.1, 68.1, 66.9, 47.7, 42.9, 21.7.

Morpholino(naphthalen-2-yl)methanone (5r).[19a] **5r** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 2:1): a white solid (233.9 mg, 97%), mp = 101.3−102.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (brs, 1H), 7.88−7.83 (m, 3H), 7.55−7.47 (m, 3H), 3.71−3.53 (m, 8H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.5, 133.8, 132.7, 132.6, 128.5, 128.4, 127.9, 127.2, 127.1, 126.8, 124.3, 66.9, 48.3, 42.7.

(3-Methylfuran-2-yl)(morpholino)methanone (5s). **5s** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a yellow solid (130.7 mg, 67%), mp = 46.2−47.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.24 (s, 1H), 3.65 (s, 8H), 2.20 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.3, 142.5, 142.0, 127.9, 114.5, 66.9, 46.7, 44.4, 11.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{13}NO_3Na$ 218.0787; Found 218.0795.

Fenfuram (5t).[19a] **5t** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a yellow solid (106.6 mg, 53%), mp = 105.6−106.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, J = 8.8, 1.2 Hz, 2H), 7.51 (brs, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 2.0 Hz, 1H), 7.12 (t, J = 7.2 Hz, 1H), 6.55 (d, J = 2.0 Hz, 1H), 2.62 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.3, 158.0, 140.6, 137.9, 129.1, 124.5, 120.4, 115.9, 108.3, 13.7.

4-(2-Methyl-furan-3-carbonyl)-morpholine (5u).[19a] **5u** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a yellow oil (119.0 mg, 61%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, J = 2.0 Hz, 1H), 6.31(d, J = 2.0

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Hz, 1H), 3.67−3.62 (m, 8H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.5, 153.9, 140.5, 115.3, 110.2, 67.1, 47.7, 42.6, 13.1.

*N-Phenylthiophene-3-carboxamide (**5v**).*[20a] **5v** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (172.6 mg, 85%), mp = 150.9−152.1 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 10.05 (brs, 1H), 8.35(t, *J* = 2.4 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.65−7.64 (m, 2H), 7.35(t, *J* = 7.2 Hz, 2H), 7.09(t, *J* = 7.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 160.9, 139.0, 137.9, 129.7, 128.6, 127.2, 126.9, 123.6, 120.3.

*5-Methyl-N-phenyloxazole-4-carboxamide (**5w**).* **5w** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a yellow liquid (185.9 mg, 92%), mp = 84.7−87.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.75 (brs, 1H), 7.73 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 2.71 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 154.3, 147.9, 137.7, 129.1, 129.0, 124.4, 119.8, 11.8. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O_2Na$ 225.0634; found 225.0641.

*2-Methyl-N-phenylthiazole-4-carboxamide (**5x**).* **5x** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a yellow solid (194.1 mg, 89%), mp = 113.5−114.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.20 (brs, 1H), 8.03 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 2.73 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.2, 159.0, 149.8, 137.9, 129.1, 124.4, 123.7, 119.8, 19.2. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{11}N_2OS$ 219.0587; Found 219.0594.

*N-Phenyl-1H-benzo[d]imidazole-6-carboxamide (**5y**).*[38] **5y** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a purple solid (87.7 mg, 37%), mp = 274.6−277.5 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 12.75 (brs, 1H), 10.22 (s, 1H), 8.37 (s, 1H), 8.29 (s, 1H), 7.86−7.80 (m, 3H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 166.0, 144.1, 139.5, 139.4, 128.65, 128.62, 128.57, 123.4, 122.4, 122.0, 120.3, 110.1.

*N,2-Diphenylacetamide (**6a**).*[19a] **6a** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (175.2 mg, 83%), mp = 116.5−117.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.43−7.36 (m, 4H), 7.34−7.24 (m, 6H), 7.07 (t, *J* = 7.2 Hz, 1H), 3.71 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.3, 137.8, 134.6, 129.6, 129.3, 129.0, 127.7, 124.6, 120.0, 44.9.

*Tetrahydro-pyran-4-carboxylic acid anilide (**6b**).*[19a] **6b** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (159.9 mg, 78%), mp = 152.7−154.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.6 Hz, 2H), 7.46 (brs, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 4.05 (d, *J* = 11.6 Hz, 2H), 3.42 (td, *J* = 11.6, 2.0 Hz, 2H), 2.53−2.45 (m, 1H), 1.97−1.77 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.8, 137.9, 129.1, 124.5, 120.1, 67.3, 43.3, 29.3.

*N-Phenylcyclohex-3-ene-1-carboxamide (**6c**).*[39] **6c** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 20:1): a white solid (166.9 mg, 83%), mp = 119.6−120.7 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (brs, 1H), 7.53(d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 5.76−5.70 (m, 2H), 2.50−2.50 (m, 1H), 2.40−2.35 (m, 1H), 2.29−2.24 (m, 1H), 2.15−2.09 (m,2H), 2.02−1.98 (m, 1H), 1.87−1.77 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.5, 138.2, 129.0, 126.9, 125.3, 124.3, 120.0, 42.3, 28.2, 25.9, 24.67.

*N-Pivaloylaniline (**6d**).*[19a] **6d** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (131.1 mg, 74%), mp = 130.1−131.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.39 (brs, 1H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 1.31 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.7, 138.1, 129.0, 124.3, 120.1, 39.7, 27.7.

*N-Phenylcinnamamide (**6e**).*[40] **6e** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (178.5 mg, 80%), mp = 153.6−155.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 15.6 Hz, 2H), 7.66−7.64 (m, 2H), 7.50−7.48 (m, 2H), 7.36−7.32 (m, 5H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.60 (d, *J* = 15.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.3, 142.5, 138.2, 134.7, 130.1, 129.2, 129.0, 128.1, 124.6, 121.0, 120.1.

*N-Benzylcinnamamide (**6f**).*[16d] **6f** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (218.2 mg, 92%), mp = 110.9−112.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 15.6 Hz, 1H), 7.44−7.41 (m, 2H), 7.31−7.26 (m, 8H), 6.61 (d, *J* = 9.6 Hz, 1H), 6.51−6.46 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.1, 141.2, 138.3, 134.8, 129.7, 128.8, 128.7, 127.9, 127.5, 120.69, 120.68, 43.8.

*N-Hexylcinnamamide (**6g**).*[16a] **6g** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (201.3 mg, 87%), mp = 37.4−38.5 °C. ^1H NMR (400 MHz, $CDCl_3$): 7.62 (d, *J* = 15.6 Hz, 1H), 7.47−7.45 (m, 2H), 7.31−7.29 (m, 3H), 6.49 (d, *J* = 15.6 Hz, 1H), 6.36 (brs, 1H), 3.39−3.34 (m, 2H), 1.56 (tt, *J* = 7.4, 7.4 Hz, 2H), 1.31−1.24 (m, 6H), 0.85 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.2, 140.6, 135.0, 129.6, 128.8, 127.8, 121.2, 39.9, 31.6, 29.7, 26.8, 22.6, 14.1.

*N-Benzyl-3-phenylpropiolamide (**6h**).*[16d] **6h** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (178.7 mg, 76%), mp = 110.2−111.5 °C. ^1H NMR (400 MHz, $CDCl_3$): 7.53−7.51 (m, 2H), 7.41−7.31 (m, 8H), 6.28 (brs, 1H), 4.54 (d, *J* = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.4, 137.4, 132.6, 130.2, 129.0, 128.6, 128.1, 127.9, 120.2, 85.3, 83.0, 44.1.

*tert-Butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate (**6i**).*[16c] **6i** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 3:1): a white solid (250.3 mg, 90%), mp = 116.5−117.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29−7.20 (m, 5H), 7.16 (brs, 1H), 5.48 (brs, 1H), 4.39−4.35 (m, 2H), 4.26 (t, *J* = 8.4 Hz, 1H), 1.38 (s, 9H), 1.32 (d, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.0, 155.6, 138.2, 128.6, 127.5, 127.3, 79.9, 50.1, 43.2, 28.3, 18.6. HPLC conditions: DAICEL CHIRALCEL AD-H column (20% MeOH−CO_2, 1.5 mL/min, 254 nm), t_R: 9.9 min (minor), 10.9 min (major).

*tert-Butyl (1-(benzylamino)-3-methyl-1-oxobutan-2-yl)-carbamate (**6j**).*[16c] **6j** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (260.26 mg, 85%), mp = 120.4−121.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26−7.17 (m, 5H), 6.48 (brs, 1H), 5.09 (brs, 1H), 4.37 (t, *J* = 6.0 Hz, 2H), 3.87 (t, *J* = 6.8 Hz, 1H), 2.06 (brs, 1H), 1.34 (s, 9H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.7, 156.1, 138.2, 128.8, 127.8, 127.6, 60.2, 43.5, 30.9, 28.4, 19.5, 18.0. HPLC conditions: DAICEL CHIRALCEL AD-H column (20% MeOH−CO_2, 1.5 mL/min, 254 nm), t_R: 9.4 min (major), 10.8 min (minor).

*N-Benzylmandelamide (**6k**).*[41] **6k** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 2:1): a white solid (176.9 mg, 83%), mp = 101.4−102.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.24 (m, 8H), 7.16−7.14 (m, 2H), 6.65 (brs, 1H), 5.01 (s, 1H), 4.43−4.32 (m, 2H), 3.87 (d, *J* = 3.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.4, 139.5, 137.8, 128.9, 128.8, 128.7, 127.7, 126.9, 74.2, 43.5. HPLC conditions: DAICEL CHIRALCEL AD-H column (20% MeOH−CO_2, 1.5 mL/min, 254 nm), t_R: 11.7 min (minor), 12.4 min (major).

*N-Phenethyloleamide (**7a**).*[42] **7a** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (296.7 mg, 77%), mp = 42.3−43.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 7.2 Hz, 2H), 7.13−7.08 (m, 3H), 5.95 (brs, 1H), 5.27−5.24 (m, 2H), 3.39 (q, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.03 (t, *J* = 7.2 Hz, 2H), 1.95−1.90 (m, 3H), 2.03 (t, *J* = 6.8 Hz, 2H), 1.21−1.18 (m, 21H), 0.81−0.78 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.3, 139.0, 129.9, 129.7, 128.7, 128.5, 126.3, 40.6, 36.6, 35.7, 31.9, 29.73, 29.69, 29.63, 29.5, 29.33, 29.28, 29.24, 29.1, 27.2, 27.1, 25.8, 22.6, 14.1.

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*8-(3-Octyloxiran-2-yl)-N-phenethyloctanamide (**7b**).*[43] **7b** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 15:1): a white solid (300.9 mg, 75%), mp = 60.1−62.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, J = 6.8 Hz, 2H), 7.23−7.17 (m, 3H), 5.57 (brs, 1H), 3.50 (q, J = 7.2 Hz, 2H), 2.90−2.87 (m, 2H), 2.80 (t, J = 6.8 Hz, 2H), 2.10 (t, J = 7.6 Hz, 2H), 1.60−1.26 (m, 26H), 0.88−0.85 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.2, 139.1, 128.8, 128.7, 126.6, 57.32, 57.29, 40.6, 36.8, 35.8, 31.9, 29.63, 29.61, 29.4, 29.33, 29.30, 29.2, 27.9, 27.9, 26.69, 26.68, 25.8, 22.8, 14.2.

*8-(3-Octyloxiran-2-yl)-N-phenyloctanamide (**7c**).* **7c** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (265.1 mg, 71%), mp = 79.4−80.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 7.6 Hz, 2H), 7.40 (brs, 1H), 7.30 (t, J = 7.6 Hz, 2H), 7.08 (t, J = 7.6 Hz, 1H), 2.93−2.88 (m, 2H), 2.34 (t, J = 7.2 Hz, 2H), 1.72−1.70 (m, 2H), 1.50−1.24 (m, 24H), 0.89−0.86 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.6, 138.2, 129.1, 124.2, 119.9, 57.4, 37.8, 32.0, 31.6, 29.67, 29.65, 29.38, 29.34, 29.31, 29.2, 28.0, 27.9, 26.73, 26.71, 25.7, 22.8, 14.2. HRMS

(ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{40}NO_2$ 374.3054; found 374.3058.

*(E)-N-Phenethyldocos-13-enamide (**7d**).* **7d** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 5:1): a white solid (357.5 mg, 81%), mp = 58.6−59.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, J = 6.8 Hz, 2H), 7.22−7.16 (m, 3H), 5.82 (brs, 1H), 5.34 (t, J = 4.8 Hz, 2H), 3.49 (dd, J = 12.8, 6.8 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.11 (t, J = 7.6 Hz, 2H), 2.04−1.99 (m, 4H), 1.59−1.55 (m, 2H), 1.35−1.25 (m, 28H), 0.88 (t, J = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.3, 139.0, 129.91, 129.88, 128.8, 128.6, 126.5, 40.6, 36.8, 35.8, 32.7, 31.9, 29.82, 29.81, 29.75, 29.68, 29.61, 29.56, 29.43, 29.36, 29.27, 29.21, 29.17, 27.2, 25.8, 25.1, 22.7, 14.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{30}H_{51}NONa$ 464.3863; found 464.3866.

*(9Z,12E)-N-Phenethyloctadeca-9,12-dienamide (**7e**).* **7e** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a yellow oil (256.8 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (t, J = 7.6 Hz, 2H), 7.24−7.17 (m, 3H), 5.57 (brs, 1H), 5.39−5.31 (m, 4H), 3.51 (q, J = 6.8 Hz, 2H), 2.83−2.75 (m, 4H), 2.11 (t, J = 7.6 Hz, 2H), 2.07−2.02 (m, 4H), 1.60−1.56 (m, 2H), 1.37−1.28 (m, 14H), 0.90−0.87 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.3, 139.0, 130.3, 130.1, 128.8, 128.7, 128.1, 128.0, 126.6, 40.6, 36.9, 35.8, 31.6, 29.7, 29.4, 29.4, 29.3, 29.2, 27.3, 25.8, 25.7, 25.0, 22.7, 14.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{26}H_{41}NONa$ 406.3080; found 406.3086.

*N-Phenethylundec-10-enamide (**7f**).*[44] **7f** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 10:1): a white solid (247.1 mg, 86%), mp = 47.5−48.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, J = 6.8 Hz, 2H), 7.23−7.17 (m, 3H), 5.82−5.74(m, 2H), 4.94 (qq, J = 12.0, 1.6 Hz, 2H), 3.49 (q, J = 6.0 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.11 (t, J = 7.2 Hz, 2H), 2.05−2.00 (m, 2H), 1.59−1.56 (m, 2H), 1.38−1.26 (m, 10H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.3, 139.1, 139.0, 128.7, 128.6, 126.4, 114.2, 40.6, 36.8, 35.7, 33.8, 29.33, 29.27, 29.1, 28.9, 25.8, 24.7.

*Methyl 4-(2-oxo-2-(phenylamino)ethyl)benzoate (**A**).*[19b] **A** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 2:1): a white solid (177.6 mg, 66%), mp = 116.5−117.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 8.4 Hz, 4H), 7.30−7.26 (m, 3H), 7.10 (t, J = 7.2 Hz, 1H), 3.92 (s, 3H), 3.76 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.3, 166.9, 139.7, 137.6, 130.4, 129.6, 129.1, 127.5, 124.8, 120.1, 52.3, 44.8.

*4-(2-Oxo-2-(phenylamino)ethyl)-N-phenylbenzamide (**B**).* **B** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 1:1): a white solid (92.4 mg, 28%), mp = 165.4−168.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.37−7.28 (m, 4H), 7.11−7.03 (m, 2H), 3.75 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 168.6, 165.4, 139.7, 139.2, 139.1, 133.3, 129.1, 128.7, 128.6, 127.7, 123.6, 123.3, 120.3, 119.1, 43.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_2O_2$ 331.1441; found 331.1464.

*N-(3-(Methylamino)propyl)benzamide (**C**).*[45] **C** was prepared according to the general procedure. Purification by column chromatography (DCM/MeOH = 10:1): a colorless liquid (163.3 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (brs, 1H), 7.76−7.74 (m, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 8.0 Hz, 2H), 4.00 (brs, 1H), 3.45 (q, J = 10.8, 5.2 Hz, 2H), 2.71 (t, J = 6.0 Hz, 2H), 2.38 (s, 3H), 1.76−1.70 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.5, 134.4, 131.1, 128.3, 126.9, 49.8, 39.0, 35.6, 27.5.

*N-(1-Hydroxypropan-2-yl)benzamide (**D**).*[46] **D** was prepared according to the general procedure. Purification by column chromatography (PE/EA = 1:1): a pink solid (154.0 mg, 86%), mp = 104.5−105.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 7.2 Hz, 2H), 7.52−7.42 (m, 3H), 4.71 (brs, 1H), 4.07−4.00 (m, 1H), 3.47 (dd, J = 10.4, 5.6 Hz, 1H), 3.35 (dd, J = 10.4, 6.4 Hz, 1H), 1.13 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 165.9, 134.8, 131.0, 128.2, 127.3, 64.4, 47.3, 17.2.

*N-(4-(2-(Dimethylamino)ethoxy)benzyl)-3,4,5-trimethoxybenzamide (**E**).*[26] **E** was prepared according to the general procedure. Purification by column chromatography (DCM/MeOH = 20:1): a colorless liquid (314.4 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.4 Hz, 2H), 7.01 (s, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.62 (m, 1H), 4.51 (d, J = 5.6 Hz, 2H), 4.04 (t, J = 5.6 Hz, 2H), 3.84 (s, 9H), 2.04 (t, J = 5.6 Hz, 2H), 2.33 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.1, 158.3, 153.2, 140.9, 130.6, 129.9, 129.3, 114.8, 104.5, 65.9, 61.0, 58.2, 56.4, 45.8, 43.7.

*N-(4-(2-(Dimethylamino)ethoxy)benzyl)-3,4-dimethoxybenzamide (**F**).*[26] **F** was prepared according to the general procedure. Purification by column chromatography (DCM/MeOH = 30:1): a colorless liquid (279.4 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 2.0 Hz, 1H), 7.28 (dd, J = 6.4, 2.0 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 4.48 (d, J = 5.6 Hz, 2H), 4.00 (t, J = 5.6 Hz, 2H), 3.84 (d, J = 4.0 Hz, 6H), 2.68 (t, J = 6.0 Hz, 2H), 2.29 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.9, 158.2, 151.7, 148.9, 130.7, 129.2, 127.1, 119.5, 114.7, 110.7, 110.2, 65.9, 58.2, 55.9, 45.8, 43.5.

Computational Details. All OF the DFT calculations were performed using the Gaussian 09 program[47] and the geometries were fully optimized at the solution phase (toluene as solvent) with the SMD solvation model.[48] The B3LYP[49] functional with SDD[50] basis set for the Mn atom and 6-31G(d,p) basis set for the other atoms was used for geometry optimization involved in the model reaction. After the structural optimizations for all of the stationary points, frequency calculations at the same level of theory were carried out to identify all of the stationary points as minima (zero imaginary frequency) or transition state (only one frequency), and to provide corrections for free energies. To obtain a more precise energy, The B3LYP-D3[51] functional with SDD basis set for Mn atom and 6-311+G(d,p) basis set for the other atoms was used to calculate the solvation single point energies to provide more accurate energy information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02478.

NMR spectra and X-ray crystallographic data of the manganese complexes; NMR spectra of the amides; HPLC spectra for **6i**,**k** and UV−vis and IR spectra for mechanism; kinetic studies for reaction order; and DFT calculations data (PDF)

Accession Codes

CCDC 1961734, 1965826, and 1965828 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/

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data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

Donghui Wei − *College of Chemistry, Center of Computational Chemistry, Zhengzhou University, Zhengzhou 450001, People's Republic of China;* orcid.org/0000-0003-2820-282X; Email: donghuiwei@zzu.edu.cn

Ning Liu − *School of Chemistry and Chemical Engineering, Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, Shihezi, Xinjiang 832003, People's Republic of China;* orcid.org/0000-0001-7299-0400; Phone: (+0086)-0993-205-7277; Email: ningliu@shzu.edu.cn, ninglau@163.com; Fax: (+0086)-0993-205-7270

Authors

Zhengqiang Fu − *School of Chemistry and Chemical Engineering, Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, Shihezi, Xinjiang 832003, People's Republic of China*

Xinghua Wang − *College of Chemistry, Center of Computational Chemistry, Zhengzhou University, Zhengzhou 450001, People's Republic of China*

Sheng Tao − *School of Chemistry and Chemical Engineering, Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, Shihezi, Xinjiang 832003, People's Republic of China*

Qingqing Bu − *School of Chemistry and Chemical Engineering, Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, Shihezi, Xinjiang 832003, People's Republic of China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02478

Author Contributions

Z.F. and N.L. performed the majority of experiments and drafted the paper. X.W. and D.W. contributed the theoretical calculations. S.T. provided his assistance in the single crystal X-ray diffraction. Q.B. proposed valuable advice for improving the paper. All authors discussed the results and commented on the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Pattabiraman, V. R.; Bode, J. W. Rethinking amide bond synthesis. *Nature* **2011**, *480*, 471−479. (b) Wang, X. Challenges and outlook for catalytic direct amidation reactions. *Nat. Catal.* **2019**, *2*, 98−102. (c) Sabatini, M. T.; Boulton, L. T.; Sneddon, H. F.; Sheppard, T. D. A green chemistry perspective on catalytic amide bond formation. *Nat. Catal.* **2019**, *2*, 10−17.

(2) Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H. Catalytic amide formation from non-activated carboxylic acids and amines. *Chem. Soc. Rev.* **2014**, *43*, 2714−2742.

(3) (a) Allen, C. L.; Williams, J. M. J. Metal-catalysed approaches to amide bond formation. *Chem. Soc. Rev.* **2011**, *40*, 3405−3415. (b) Valeur, E.; Bradley, M. Amide bond formation: beyond the myth of coupling reagents. *Chem. Soc. Rev.* **2009**, *38*, 606−631. (c) Dunetz, J. R.; Magano, J.; Weisenburger, G. A. Large-Scale Applications of Amide Coupling Reagents for the Synthesis of Pharmaceuticals. *Org. Process Res. Dev.* **2016**, *20*, 140−177.

(4) Filonenko, G. A.; van Putten, R.; Hensen, E. J. M.; Pidko, E. A. Catalytic (de)hydrogenation promoted by non-precious metals-Co, Fe and Mn: recent advances in an emerging field. *Chem. Soc. Rev.* **2018**, *47*, 1459−1483.

(5) (a) Daw, P.; Kumar, A.; Espinosa-Jalapa, N. A.; Ben-David, Y.; Milstein, D. Direct Synthesis of Amides by Acceptorless Dehydrogenative Coupling of Benzyl Alcohols and Ammonia Catalyzed by a Manganese Pincer Complex: Unexpected Crucial Role of Base. *J. Am. Chem. Soc.* **2019**, *141*, 12202−12206. (b) Kumar, A.; Espinosa-Jalapa, N. A.; Leitus, G.; Diskin-Posner, Y.; Avram, L.; Milstein, D. Direct Synthesis of Amides by Dehydrogenative Coupling of Amines with either Alcohols or Esters: Manganese Pincer Complex as Catalyst. *Angew. Chem., Int. Ed.* **2017**, *56*, 14992−14996. (c) Chakraborty, S.; Gellrich, U.; Diskin-Posner, Y.; Leitus, G.; Avram, L.; Milstein, D. Manganese-Catalyzed N-Formylation of Amines by Methanol Liberating H2: A Catalytic and Mechanistic Study. *Angew. Chem., Int. Ed.* **2017**, *56*, 4229−4233. (d) Espinosa-Jalapa, N. A.; Kumar, A.; Leitus, G.; Diskin-Posner, Y.; Milstein, D. Synthesis of Cyclic Imides by Acceptorless Dehydrogenative Coupling of Diols and Amines Catalyzed by a Manganese Pincer Complex. *J. Am. Chem. Soc.* **2017**, *139*, 11722−11725. (e) Garbe, M.; Junge, K.; Beller, M. Homogeneous Catalysis by Manganese-Based Pincer Complexes. *Eur. J. Org. Chem.* **2017**, *2017*, 4344−4362. (f) Mondal, A.; Subaramanian, M.; Nandakumar, A.; Balaraman, E. Manganese-Catalyzed Direct Conversion of Ester to Amide with Liberation of H_2. *Org. Lett.* **2018**, *20*, 3381−3384.

(6) (a) Gunanathan, C.; Ben-David, Y.; Milstein, D. Direct Synthesis of Amides from Alcohols and Amines with Liberation of H_2. *Science* **2007**, *317*, 790−792. (b) Nordstrøm, L. U.; Vogt, H.; Madsen, R. Amide Synthesis from Alcohols and Amines by the Extrusion of Dihydrogen. *J. Am. Chem. Soc.* **2008**, *130*, 17672−17673. (c) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. Ruthenium-Catalyzed Oxidation of Alcohols into Amides. *Org. Lett.* **2009**, *11*, 2667−2670. (d) Shu, S.; Huang, M.; Jiang, J.; Qu, L.-B.; Liu, Y.; Ke, Z. Catalyzed or non-catalyzed: chemoselectivity of Ru-catalyzed acceptorless dehydrogenative coupling of alcohols and amines via metal−ligand bond cooperation and (de)aromatization. *Catal. Sci. Technol.* **2019**, *9*, 2305−2314. (e) Muthaiah, S.; Ghosh, S. C.; Jee, J.-E.; Chen, C.; Zhang, J.; Hong, S. H. Direct Amide Synthesis from Either Alcohols or Aldehydes with Amines: Activity of Ru(II) Hydride and Ru(0) Complexes. *J. Org. Chem.* **2010**, *75*, 3002−3006. (f) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. Direct Amide Synthesis from Alcohols and Amines by Phosphine-Free Ruthenium Catalyst Systems. *Adv. Synth. Catal.* **2009**, *351*, 2643−2649. (g) Prades, A.; Peris, E.; Albrecht, M. Oxidations and Oxidative Couplings Catalyzed by Triazolylidene Ruthenium. Complexes. *Organometallics* **2011**, *30*, 1162−1167.

(7) Zweifel, T.; Naubron, J.-V.; Grützmacher, H. Catalyzed Dehydrogenative Coupling of Primary Alcohols with Water, Methanol, or Amines. *Angew. Chem., Int. Ed.* **2009**, *48*, 559−563.

(8) Spasyuk, D.; Vicent, C.; Gusev, D. G. Chemoselective Hydrogenation of Carbonyl Compounds and Acceptorless Dehydro-

genative Coupling of Alcohols. *J. Am. Chem. Soc.* **2015**, *137*, 3743−3746.
(9) Lane, E. M.; Hazari, N.; Bernskoetter, W. H. Iron-catalyzed urea synthesis: dehydrogenative coupling of methanol and amines. *Chem. Sci.* **2018**, *9*, 4003−4008.
(10) Shimizu, K.-i.; Ohshima, K.; Satsuma, A. Direct Dehydrogenative Amide Synthesis from Alcohols and Amines Catalyzed by γ-Alumina Supported Silver Cluster. *Chem. - Eur. J.* **2009**, *15*, 9977−9980.
(11) (a) Song, W.; Dong, K.; Li, M. Visible Light-Induced Amide Bond Formation. *Org. Lett.* **2020**, *22*, 371. (b) Liu, H.; Zhao, L.; Yuan, Y.; Xu, Z.; Chen, K.; Qiu, S.; Tan, H. Potassium Thioacids Mediated Selective Amide and Peptide Constructions Enabled by Visible Light Photoredox Catalysis. *ACS Catal.* **2016**, *6*, 1732−1736. (c) Das, S.; Ray, S.; Ghosh, A. B.; Samanta, P. K.; Samanta, S.; Adhikary, B.; Biswas, P. Visible light driven amide synthesis in water at room temperature from Thioacid and amine using CdS nanoparticles as heterogeneous Photocatalyst. *Appl. Organomet. Chem.* **2018**, *32*, e4199.
(12) Takise, R.; Muto, K.; Yamaguchi, J. Cross-coupling of aromatic esters and amides. *Chem. Soc. Rev.* **2017**, *46*, 5864−5888.
(13) (a) Caldwell, N.; Jamieson, C.; Simpson, I.; Tuttle, T. Organobase-Catalyzed Amidation of Esters with Amino Alcohols. *Org. Lett.* **2013**, *15*, 2506−2509. (b) Movassaghi, M.; Schmidt, M. A. N-Heterocyclic Carbene-Catalyzed Amidation of Unactivated Esters with Amino Alcohols. *Org. Lett.* **2005**, *7*, 2453−2456. (c) Caldwell, N.; Jamieson, C.; Simpson, I.; Watson, A. J. B. Catalytic amidation of unactivated ester derivatives mediated by trifluoroethanol. *Chem. Commun.* **2015**, *51*, 9495−9498.
(14) (a) Tsuji, H.; Yamamoto, H. Hydroxy-Directed Amidation of Carboxylic Acid Esters Using a Tantalum Alkoxide Catalyst. *J. Am. Chem. Soc.* **2016**, *138*, 14218−14221. (b) Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. Lanthanum(III) Triflate Catalyzed Direct Amidation of Esters. *Org. Lett.* **2014**, *16*, 2018−2021. (c) Ali, M. A.; Siddiki, S. M. A. H.; Kon, K.; Shimizu, K.-I. A Heterogeneous Niobium(V) Oxide Catalyst for the Direct Amidation of Esters. *ChemCatChem* **2015**, *7*, 2705−2710. (d) Sultan, S.; Kumar, M.; Devari, S.; Mukherjee, D.; Ali Shah, B. Copper−Manganese Spinel Oxide Catalyzed Synthesis of Amides and Azobenzenes via Aminyl Radical Cations. *ChemCatChem* **2016**, *8*, 703−707. (e) Lenstra, D. C.; Nguyen, D. T.; Mecinović, J. Zirconium-catalyzed direct amide bond formation between carboxylic esters and amines. *Tetrahedron* **2015**, *71*, 5547−5553. (f) Muramatsu, W.; Hattori, T.; Yamamoto, H. Substrate-Directed Lewis-Acid Catalysis for Peptide Synthesis. *J. Am. Chem. Soc.* **2019**, *141*, 12288−12295. (g) Nagae, H.; Hirai, T.; Kato, D.; Soma, S.; Akebi, S. Y.; Mashima, K. Dinuclear manganese alkoxide complexes as catalysts for C-N bond cleavage of simple tertiary N,N-dialkylamides to give esters. *Chem. Sci.* **2019**, *10*, 2860−2868. (h) Hirai, T.; Kato, D.; Mai, B. K.; Katayama, S.; Akiyama, S.; Nagae, H.; Himo, F.; Mashima, K. Esterification of Tertiary Amides: Remarkable Additive Effects of Potassium Alkoxides for Generating Hetero Manganese−Potassium Dinuclear Active Species. *Chem. - Eur. J.* **2020**, *26*, 10735−10742. (i) Nguyen, D. T.; Lenstra, D. C.; Mecinović, J. Chemoselective calcium-catalysed direct amidation of carboxylic esters. *RSC Adv.* **2015**, *5*, 77658−77661.
(15) de Figueiredo, R. M.; Suppo, J.-S.; Campagne, J.-M. Nonclassical Routes for Amide Bond Formation. *Chem. Rev.* **2016**, *116*, 12029−12122.
(16) (a) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A. Catalytic Ester−Amide Exchange Using Group (IV) Metal Alkoxide−Activator Complexes. *J. Am. Chem. Soc.* **2005**, *127*, 10039−10044. (b) Sabot, C.; Kumar, K. A.; Meunier, S.; Mioskowski, C. A convenient aminolysis of esters catalyzed by 1,5,7-triazabicyclo[4.4.0] dec-5-ene (TBD) under solvent-free conditions. *Tetrahedron Lett.* **2007**, *48*, 3863−3866. (c) Ohshima, T.; Hayashi, Y.; Agura, K.; Fujii, Y.; Yoshiyama, A.; Mashima, K. Sodium methoxide: a simple but highly efficient catalyst for the direct amidation of esters. *Chem. Commun.* **2012**, *48*, 5434−5436. (d) Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. Lanthanum(III) triflate catalyzed direct amidation of esters. *Org. Lett.* **2014**, *16*, 2018−2021.
(17) Hie, L.; Fine Nathel, N. F.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Garg, N. K. Nickel-Catalyzed Activation of Acyl C−O Bonds of Methyl Esters. *Angew. Chem., Int. Ed.* **2016**, *55*, 2810−2814.
(18) Ben Halima, T.; Vandavasi, J. K.; Shkoor, M.; Newman, S. G. A Cross-Coupling Approach to Amide Bond Formation from Esters. *ACS Catal.* **2017**, *7*, 2176−2180.
(19) (a) Ben Halima, T.; Masson-Makdissi, J.; Newman, S. G. Nickel-Catalyzed Amide Bond Formation from Methyl Esters. *Angew. Chem., Int. Ed.* **2018**, *57*, 12925−12929. (b) Zheng, Y.-L.; Newman, S. G. Methyl Esters as Cross-Coupling Electrophiles: Direct Synthesis of Amide Bonds. *ACS Catal.* **2019**, *9*, 4426−4433.
(20) (a) Li, G.; Szostak, M. Highly selective transition-metal-free transamidation of amides and amidation of esters at room temperature. *Nat. Commun.* **2018**, *9*, 4165. (b) Li, G.; Ji, C.-L.; Hong, X.; Szostak, M. Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N−C/O−C Cleavage. *J. Am. Chem. Soc.* **2019**, *141*, 11161−11172.
(21) Cheung, C. W.; Ploeger, M. L.; Hu, X. Direct amidation of esters with nitroarenes. *Nat. Commun.* **2017**, *8*, 14878.
(22) (a) Fleckhaus, A.; Mousa, A. H.; Lawal, N. S.; Kazemifar, N. K.; Wendt, O. F. Aromatic PCN Palladium Pincer Complexes. Probing the Hemilability through Reactions with Nucleophiles. *Organometallics* **2015**, *34*, 1627−1634. (b) Bailey, W. D.; Luconi, L.; Rossin, A.; Yakhvarov, D.; Flowers, S. E.; Kaminsky, W.; Kemp, R. A.; Giambastiani, G.; Goldberg, K. I. Pyrazole-Based PCN Pincer Complexes of Palladium(II): Mono- and Dinuclear Hydroxide Complexes and Ligand Rollover C−H Activation. *Organometallics* **2015**, *34*, 3998−4010.
(23) Braunstein, P.; Naud, F. Hemilability of Hybrid Ligands and the Coordination Chemistry of Oxazoline-Based Systems. *Angew. Chem., Int. Ed.* **2001**, *40*, 680−699.
(24) (a) Liu, N.; Xie, Y.-F.; Wang, C.; Li, S.-J.; Wei, D.; Li, M.; Dai, B. Cooperative Multifunctional Organocatalysts for Ambient Conversion of Carbon Dioxide into Cyclic Carbonates. *ACS Catal.* **2018**, *8*, 9945−9957. (b) Chen, F.; Zhang, Q.-C.; Wei, D.; Bu, Q.; Dai, B.; Liu, N. Highly Stereo-Controlled Synthesis of Fatty Acid-Derived Cyclic Carbonates by Using Iron(II) Complex and Nucleophilic Halide. *J. Org. Chem.* **2019**, *84*, 11407−11416. (c) Chen, F.; Liu, N.; Dai, B. Iron(II) Bis-CNN Pincer Complex-Catalyzed Cyclic Carbonate Synthesis at Room Temperature. *ACS Sustainable Chem. Eng.* **2017**, *5*, 9065−9075. (d) Tao, S.; Guo, C.; Liu, N.; Dai, B. Counteranion-Controlled Ag2O-Mediated Benzimidazolium Ring Opening and Its Application in the Synthesis of Palladium Pincer-Type Complexes. *Organometallics* **2017**, *36*, 4432−4442. (e) Chen, F.; Chen, D.; Shi, L.; Liu, N.; Dai, B. Fiddler crab-type" imidazolium salt as remote substituents tuning organocatalyst for the cycloaddition of epoxides with carbon dioxide. *J. CO2 Util.* **2016**, *16*, 391−398. (f) Wang, Y.-B.; Liu, B.-Y.; Bu, Q.; Dai, B.; Liu, N. In Situ Ring-Closing Strategy for Direct Synthesis of N-Heterocyclic Carbene Nickel Complexes and Their Application in Coupling of Allylic Alcohols with Aryl Boronic Acids. *Adv. Synth. Catal.* **2020**, *362*, 2930−2940.
(25) Cheung, C. W.; Shen, N.; Wang, S.-P.; Ullah, A.; Hu, X.; Ma, J.-A. Manganese-mediated reductive amidation of esters with nitroarenes. *Org. Chem. Front.* **2019**, *6*, 756−761.
(26) (a) Das, J.; Banerjee, D. Nickel-Catalyzed Phosphine Free Direct N-Alkylation of Amides with Alcohols. *J. Org. Chem.* **2018**, *83*, 3378−3384. (b) Nielsen, S. D.; Smith, G.; Begtrup, M.; Kristensen, J. L. Synthesis and application of a new fluorous-tagged ammonia equivalent. *Chem. - Eur. J.* **2010**, *16*, 4557−4566.
(27) (a) Stanton, C. J., 3rd; Vandezande, J. E.; Majetich, G. F.; Schaefer, H. F., 3rd; Agarwal, J. Mn-NHC Electrocatalysts: Increasing pi Acidity Lowers the Reduction Potential and Increases the Turnover Frequency for CO_2 Reduction. *Inorg. Chem.* **2016**, *55*, 9509−9512. (b) Agarwal, J.; Stanton, C. J., 3rd; Shaw, T. W.; Vandezande, J. E.; Majetich, G. F.; Bocarsly, A. B.; Schaefer, H. F., 3rd Exploring the

https://dx.doi.org/10.1021/acs.joc.0c02478
J. Org. Chem. 2021, 86, 2339−2358

effect of axial ligand substitution (X = Br, NCS, CN) on the photodecomposition and electrochemical activity of [MnX(N−C)$(CO)_3$] complexes. *Dalton Trans.* **2015**, *44*, 2122−2131.
(28) Peng, J. B.; Li, D.; Geng, H. Q.; Wu, X. F. Palladium-Catalyzed Amide Synthesis via Aminocarbonylation of Arylboronic Acids with Nitroarenes. *Org. Lett.* **2019**, *21*, 4878−4881.
(29) Tang, L.; Matuska, J. H.; Huang, Y. H.; He, Y. H.; Guan, Z. Amide Synthesis from Thiocarboxylic Acids and Amines by Spontaneous Reaction and Electrosynthesis. *ChemSusChem* **2019**, *12*, 2570−2575.
(30) Chen, Z.; Wen, X.; Zheng, W.; He, R.; Chen, D.; Cao, D.; Long, L.; Ye, M. Acyl Cyanides as Bifunctional Reagent: Application in Copper-Catalyzed Cyanoamidation and Cyanoesterification Reaction. *J. Org. Chem.* **2020**, *85*, 5691−5701.
(31) Yi, X.; Lei, S.; Liu, W.; Che, F.; Yu, C.; Liu, X.; Wang, Z.; Zhou, X.; Zhang, Y. Copper-Catalyzed Radical N-Demethylation of Amides Using N-Fluorobenzenesulfonimide as an Oxidant. *Org. Lett.* **2020**, *22*, 4583−4587.
(32) Sawant, D. N.; Bagal, D. B.; Ogawa, S.; Selvam, K.; Saito, S. Diboron-Catalyzed Dehydrative Amidation of Aromatic Carboxylic Acids with Amines. *Org. Lett.* **2018**, *20*, 4397−4400.
(33) Li, G.-X.; Hu, X.; He, G.; Chen, G. Photoredox-Mediated Minisci-type Alkylation of N-Heteroarenes with Alkanes with High Methylene Selectivity. *ACS Catal.* **2018**, *8*, 11847−11853.
(34) Xu, X.; Feng, H.; Huang, L.; Liu, X. Direct Amidation of Carboxylic Acids through an Active α-Acyl Enol Ester Intermediate. *J. Org. Chem.* **2018**, *83*, 7962−7969.
(35) Ke, F.; Xu, Y.; Zhu, S.; Lin, X.; Lin, C.; Zhou, S.; Su, H. Electrochemical N-acylation synthesis of amides under aqueous conditions. *Green Chem.* **2019**, *21*, 4329−4333.
(36) Hwang, S.; Choi, S. Y.; Lee, J. H.; Kim, S.; In, J.; Ha, S. K.; Lee, E.; Kim, T. Y.; Kim, S. Y.; Choi, S.; Kim, S. Identification of a potent and noncytotoxic inhibitor of melanin production. *Bioorg. Med. Chem.* **2010**, *18*, 5602−5609.
(37) Krabbe, S. W.; Chan, V. S.; Franczyk, T. S.; Shekhar, S.; Napolitano, J. G.; Presto, C. A.; Simanis, J. A. Copper-Catalyzed Aerobic Oxidative Amidation of Benzyl Alcohols. *J. Org. Chem.* **2016**, *81*, 10688−10697.
(38) Gonzalez-Vera, J. A.; Medina, R. A.; Martin-Fontecha, M.; Gonzalez, A.; de la Fuente, T.; Vazquez-Villa, H.; Garcia-Carceles, J.; Botta, J.; McCormick, P. J.; Benhamu, B.; Pardo, L.; Lopez-Rodriguez, M. L. A new serotonin 5-HT6 receptor antagonist with procognitive activity - Importance of a halogen bond interaction to stabilize the binding. *Sci. Rep.* **2017**, *7*, 41293.
(39) Iosub, A. V.; Stahl, S. S. Palladium-Catalyzed Aerobic Oxidative Dehydrogenation of Cyclohexenes to Substituted Arene Derivatives. *J. Am. Chem. Soc.* **2015**, *137*, 3454−3457.
(40) Tan, E. W.; Chan, B.; Blackman, A. G. A Polar Effects Controlled Enantioselective 1,2-Chlorine Atom Migration via a Chlorine-Bridged Radical Intermediate. *J. Am. Chem. Soc.* **2002**, *124*, 2078−2079.
(41) Dineen, T. A.; Zajac, M. A.; Myers, A. G. Efficient Transamidation of Primary Carboxamides by in Situ Activation with N,N-Dialkylformamide Dimethyl Acetals. *J. Am. Chem. Soc.* **2006**, *128*, 16406−16409.
(42) Tian, J.; Gao, W.-C.; Zhou, D.-M.; Zhang, C. Recyclable Hypervalent Iodine(III) Reagent Iodosodilactone as an Efficient Coupling Reagent for Direct Esterification, Amidation, and Peptide Coupling. *Org. Lett.* **2012**, *14*, 3020−3023.
(43) Ogawa, T.; Hikasa, T.; Ikegami, T.; Ono, N.; Suzuki, H. Hitomi Electron-rich triarylbismuthines as selective condensation reagent under neutral conditions. Condensation of aliphatic carboxylic acids with amines and alcohols. *Chem. Lett.* **1993**, *22*, 815−818.
(44) Tam, E. K. W.; Rita; Liu, L. Y.; Chen, A. 2-Furanylboronic Acid as an Effective Catalyst for the Direct Amidation of Carboxylic Acids at Room Temperature. *Eur. J. Org. Chem.* **2015**, *2015*, 1100−1107.
(45) Manoury, P. M.; Binet, J. L.; Dumas, A. P.; Lefevre-Borg, F.; Cavero, I. Synthesis and antihypertensive activity of a series of 4-amino-6,7-dimethoxyquinazoline derivatives. *J. Med. Chem.* **1986**, *29*, 19−25.
(46) Nakafuku, K. M.; Fosu, S. C.; Nagib, D. A. Catalytic Alkene Difunctionalization via Imidate Radicals. *J. Am. Chem. Soc.* **2018**, *140*, 11202−11205.
(47) Frisch, M. J; et al. *Gaussian 09*, revision B.01; Gaussian, Inc.: Wallingford, CT, 2010.
(48) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.
(49) (a) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789.
(50) Dolg, M.; Wedig, U.; Stoll, H.; Preuss, H. Energy-adjusted ab initio pseudopotentials for the first row transition elements. *J. Chem. Phys.* **1987**, *86*, 866−872.
(51) (a) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* **2010**, *132*, 154104. (b) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the damping function in dispersion corrected density functional theory. *J. Comput. Chem.* **2011**, *32*, 1456−1465.

https://dx.doi.org/10.1021/acs.joc.0c02478
J. Org. Chem. 2021, 86, 2339−2358