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Ligand-controlled chemoselective nickel-catalyzed cross-electrophile coupling of cyclic anhydrides with alkyl bromides

Tingzhi Lin,[a] Junlong Jia,†[a] Yu Wu,†[b] Ziheng Li,†[a] Xueying Gao,[a] Junyu Ma,[a] Mengjiao Wei,[a] Yifei Song,[a] Zifan Wang,[a] Xinrui Yuan,[a] Patrick J. Walsh *[b] and Jianyou Mao *[a]

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The introduction of chemoselective transition-metal-catalyzed cross-electrophile coupling approaches continues to expand chemists' pallet of C–C bond-forming reactions. Herein, a Ni-catalyzed ligand-controlled divergent chemoselective cross-electrophile coupling reaction of *meso*-anhydrides with unactivated alkyl bromides has been developed. Depending on the choice of ligand, both γ-keto acid and decarbonylated β-alkylated acid derivatives were obtained from the same feedstocks with excellent selectivity. The utility of these divergent transformations was demonstrated by their broad functional group tolerance and applications in the synthesis of bioactive carboxylic acids.

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Introduction

Transition-metal-catalyzed chemoselective cross-coupling reactions of environmentally friendly carboxylic acid derivatives are among the most practical and efficient methods to construct C–C bonds,[1–3] as demonstrated by their widespread applications in pharmaceuticals and natural product synthesis.[4–8] Along these lines, the reactivity and scope of acid halides,[9,10] esters,[11,12] thioesters,[13,14] acyclic anhydrides[15] and many others have been explored to provide ketone products through direct acylation (Fig. 1A, right).[16,17] On the other hand, transition-metal-catalyzed decarbonylative arylation,[18–20] amination,[21,22] borylation,[23–26] phosphorylation,[27] and intramolecular functionalization[28–35] of carboxylic acid derivatives have also been developed[36,37] (Fig. 1A, left).

Despite considerable advances in this area, there remains room for improvement on both sides. For example, the suppression of unwanted CO deinsertion in the acylation continues to be a challenge.[38–40] Meanwhile, the characteristics that impact the decarbonylative process are not fully understood, and such cross-couplings are generally limited to C(sp^3)-based coupling partners. Therefore, the demand for straightforward methods for both the acylation and the decarbonylative alkylation of carboxylic acid derivatives remains high. The use of anhydride electrophiles is beneficial because both the reaction manifolds could be accessed, with one leading to keto acids through acylation and the other forming the decarbonylated acid products. In prior efforts in this area, Rueping and colleagues developed the chemoselective decarbonylative alkylation of aromatic esters using organozinc[41] and organoboron reagents[42] as alkyl nucleophiles. However, the use of stable and inexpensive alkyl electrophiles as coupling partners is rare.

With the aim of circumventing the use of preformed organometallic reagents, Liang and colleagues disclosed a nickel catalyzed decarbonylative alkylation of activated aryl acid chlorides with alkyl electrophiles (Fig. 1B).[43] It should be noted that Weix and Cernak developed a nickel catalyzed decarbonylative alkylation of activated carboxylic acids (*via* 2-pyridyl esters[44] and *N*-acyl-glutarimides[45]) with activated alkyl reagents (such as *N*-alkyl pyridinium salts).

In 2024, Weix and co-workers reported a nickel-catalyzed decarbonylative approach for C(sp^3)–C(sp^3) bond formation using 2-pyridyl esters and alkyl iodide electrophiles (Fig. 1C).[46] Mechanistic studies revealed that the key monoalkylnickel(II) intermediates were formed by oxidative addition of the pyridyl ester followed by decarbonylation of the resulting acyl intermediate to release CO. Furthermore, it was found that the ligand bis(4-methylpyrazole)pyridine accelerated the decarbonylation process. This important discovery serves as a guide to design decarbonylation of acyl-Ni^{II} intermediates that can be used for C(sp^3)–C(sp^3) bond formation.

[a]*School of Chemistry and Molecular Engineering, Nanjing Tech University, 30 South Puzhu Road, Nanjing 211816, P. R. China. E-mail: ias_jymao@njtech.edu.cn*
[b]*Roy and Diana Vagelos Laboratories, Penn/Merck Laboratory for High-Throughput Experimentation, University of Pennsylvania, Department of Chemistry, 231 South 34th Street, Philadelphia, Pennsylvania 19104, USA. E-mail: pwalsh@sas.upenn.edu*
†J. L. J., Y. W., and Z. H. L. contributed equally to this work.

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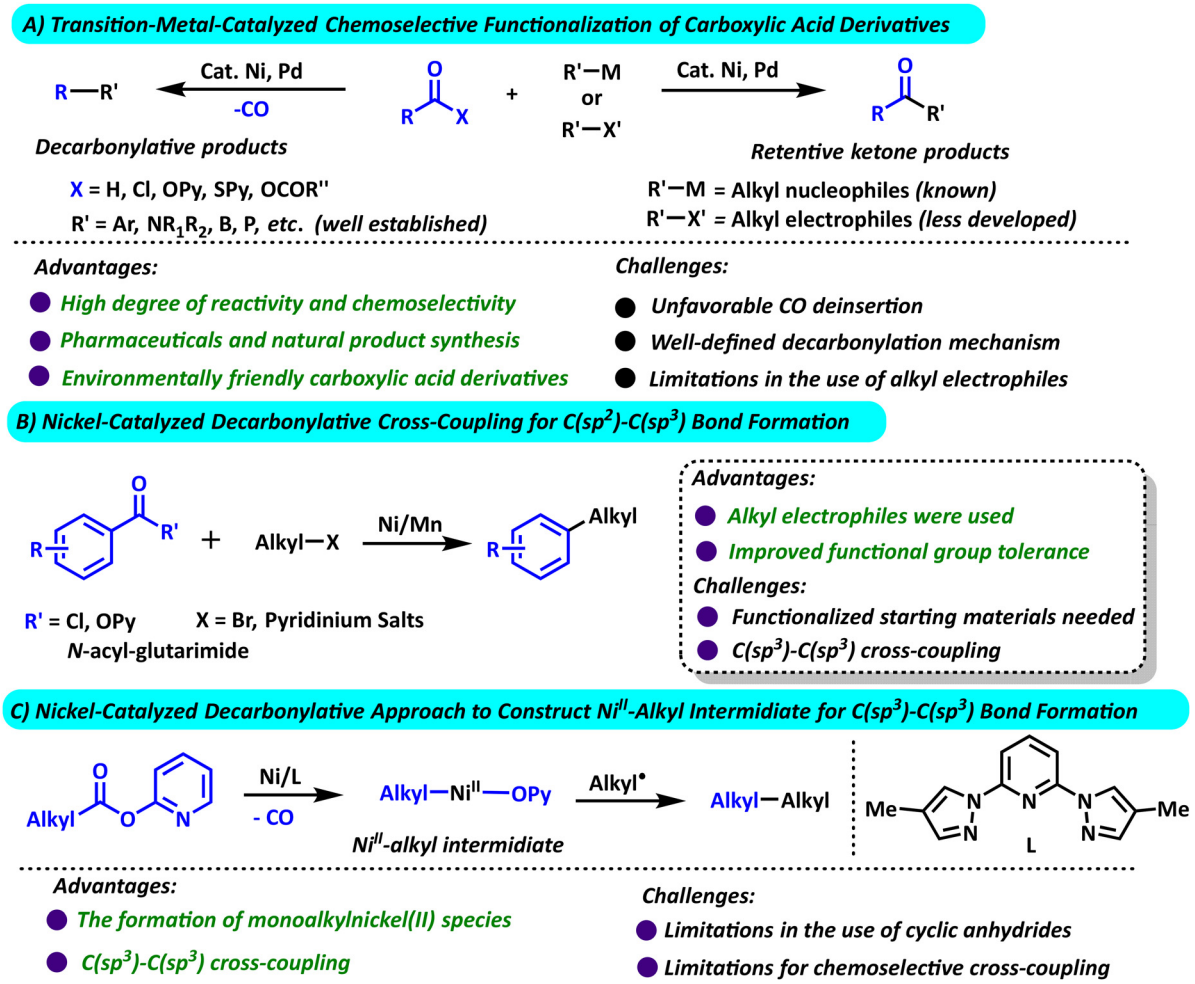

Fig. 1 Prior work. (A) Transition-metal-catalyzed chemoselective functionalization of carboxylic acid derivatives. (B) Nickel-catalyzed decarbonylative alkylation of aryl electrophiles. (C) Nickel-catalyzed decarbonylative approach to generate Ni^{II}-alkyl intermediates for $C(sp^3)$–$C(sp^3)$ bond formation.

We are interested in the functionalization of simple and readily available feedstocks *via* an anhydride desymmetrization cross-electrophile coupling (DCEC) strategy. We previously introduced a nickel-catalyzed method for coupling anhydrides with aryl triflates (Fig. 2A, left).[47] We also disclosed a nickel catalyzed $C(sp^3)$–$C(sp^3)$ decarbonylative reductive cross-electrophile coupling of homoenolates and their higher homologues with unactivated alkyl bromides (Fig. 2A, right).[48] Unfortunately, only simple monocyclic anhydrides were viable in this reaction.

Building on our initial studies, we sought to investigate a nickel catalyzed alkylation of bicyclic anhydrides with unactivated alkyl bromides under reductive conditions. A goal of this work was to control chemoselective reaction manifolds to generate either γ-keto acid derivatives or β-alkylated acid derivatives by identifying catalysts that would promote CO retention or decarbonylation, respectively. Such a process could avoid air- and water-sensitive organometallic reagents and replace activated carboxylic acids and activated alkyl reagents with simple commercially available starting materials.

Herein, we report a nickel-catalyzed ligand-controlled site-selective cross-electrophile coupling of readily available bicyclic anhydrides with unactivated alkyl bromides (Fig. 2C). The simple bidentate bipy ligand (**L1**) favors the direct acyl cross-coupling of anhydrides and alkyl bromides, providing ketone derivatives with high yields and broad functional group tolerance. In contrast, the bisoxazoline (Box) ligand **L5** favors the decarbonylative reductive cross-coupling reactions, offering the alkylated acid derivatives *via* Ni–O-homoenolates with excellent chemoselectivity. Mechanistic studies point to chelated alkyl nickel(II)-**L5** intermediates (Ni-homoenolate) formed by a $2e^-$ oxidative addition of cyclic anhydrides to $(L_n)Ni^0$ followed by decarbonylation,[49] which avoids the formation of ketone products.[50–54] Additionally, the alkyl nickel(II) intermediates are resistant to β-hydride elimination and isomerization processes,[55,56] and provide the decarbonylative products with good to excellent yields.

During the preparation of this manuscript, a related study by the team of Sigman, Reisman and co-workers appeared

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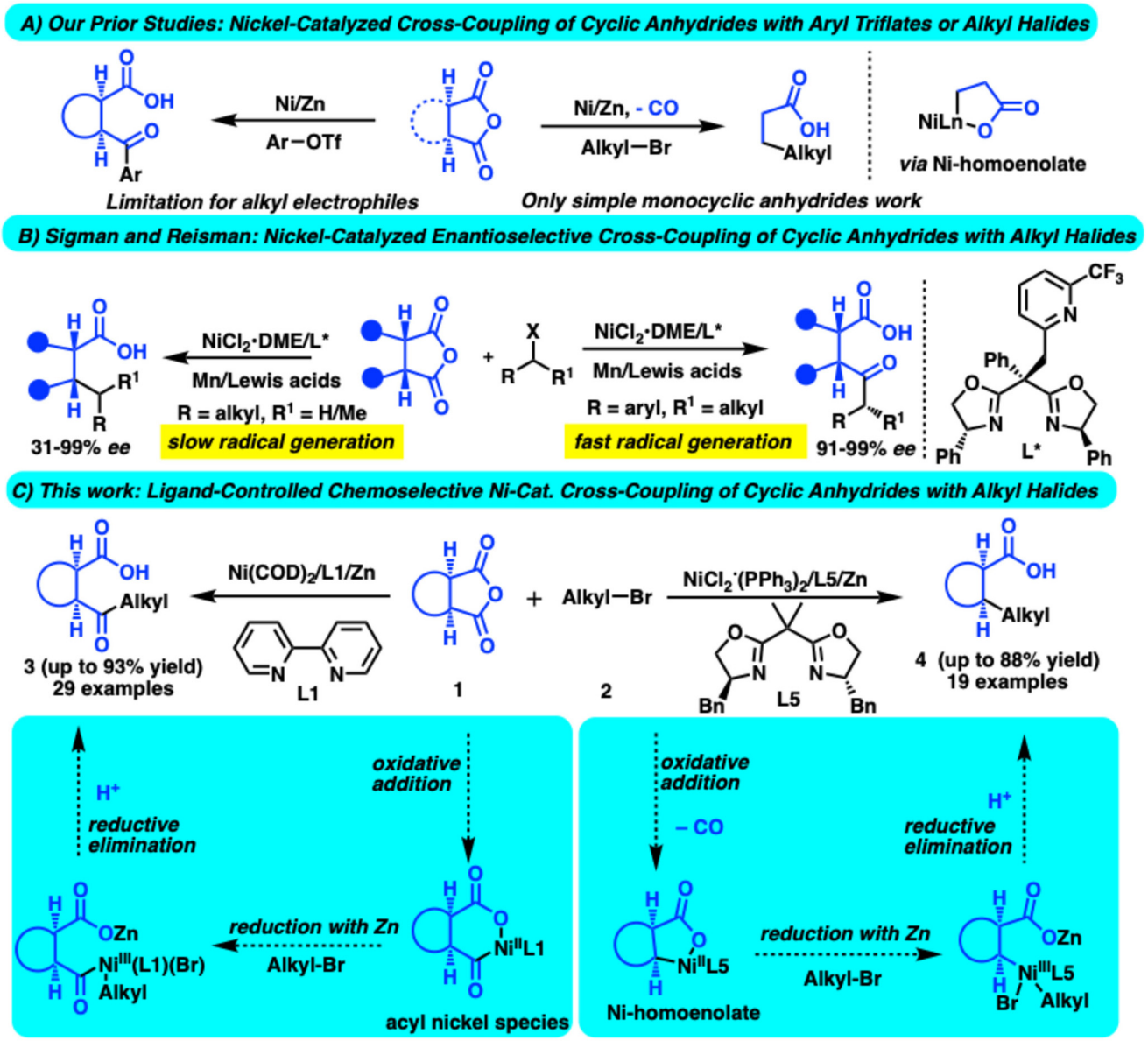

Fig. 2 Prior results from our team and the current study. (A) Our prior studies of nickel-catalyzed cross-coupling of cyclic anhydrides with aryl triflates or alkyl halides. (B) Nickel-catalyzed enantioselective cross-coupling of cyclic anhydrides with alkyl halides. (C) This work: ligand-controlled chemoselective nickel-catalyzed cross-coupling of cyclic anhydrides with alkyl halides.

using *meso*-cyclic anhydride substrates and secondary benzylic chlorides or alkyl bromides. Reactions were performed in the presence of Lewis acids, the $Ni(COD)_2$ pre-catalyst, and enantioenriched unsymmetrical bis(oxazoline) ligands with Mn as the reducing agent.[57] Interestingly, they found that the nature of the alkyl halide dictated the reaction pathway. Secondary benzylic chlorides participate in a doubly stereoselective acyl cross-coupling, yielding ketone products with catalyst control over three newly formed stereogenic centers with 91–99% ee (Fig. 2B, right). In contrast, primary alkyl halides undergo decarbonylative alkylation to afford enantioenriched β-alkyl acids with 31–99% ee (Fig. 2B, left).

Results

Reaction discovery and optimizations

To initiate the optimization of the decarbonylative cross electrophile coupling (DCEC), *cis*-1,2-cyclohexanedicarboxylic anhydride **1a** and cyclohexyl bromide **2a** were chosen as the model substrates. We used the combination of $Ni(COD)_2$/bipy (**L1**) as the catalyst precursors, dimethylacetamide (DMA) as the solvent and zinc powder as the reductant. The reaction was conducted for 12 h at 80 °C. Under these conditions, the alkylated γ-keto acid **3aa** was obtained in 22% isolated yield (Table 1, entry 1). In order to improve the efficiency of this

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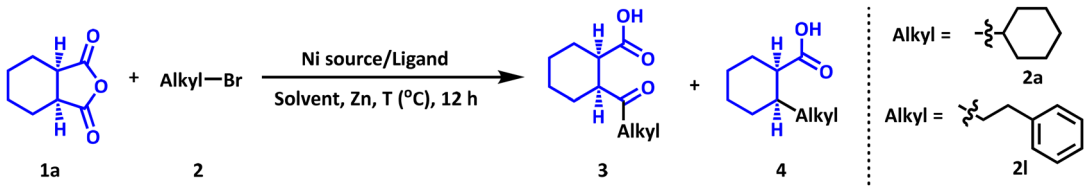
transformation, we examined the nickel source and found that $Ni(COD)_2$ was the best pre-catalyst for this reaction system (for details on nickel source screening, see Table S1). We next examined different solvents (DMF and DMSO); however, no product was recovered (Table 1, entries 3 and 4; for details on solvent screening, see Table S2). At this point, DMA was the best solvent and was used going forward.

We next decreased the amount of cyclohexyl bromide (**2a**) from 2.0 to 1.5 to 1.0 equiv. and found that 1.0 equiv. was better, affording the desired product in 45% yield (Table 1, entry 5). We, therefore, increased the amount of anhydride **1a** while employing 1 equiv. of cyclohexyl bromide (**2a**) at 0.4 M in DMA (Table 1, entries 6 and 7). These experiments indicated that 1.5 equiv. of anhydride **1a** and 1.0 equiv. of **2a** showed improved conversion (Table 1, entry 6). The amount of the zinc powder was also examined under the conditions shown in entry 6 (Table 1, entries 8 and 9). It was found that 2.0 equiv. of zinc improved the yield to 56% (Table 1, entry 8). The reaction concentration can impact the activity in the DCEC. Varying the concentration from 0.4 M to 0.5 M, 1 M, 1.3 M and 2 M (Table 1, entries 10–13) revealed that 1.3 M resulted in higher yield (78%, Table 1, entry 12). Notably, employing an alkyl chloride as the coupling partner led to a diminished yield of **3aa** (46%), while alkyl iodides gave slightly lower yields than alkyl bromides, affording the cross-coupling product in 72% yield (see Table S6). Therefore, alkyl bromides were chosen as the preferred coupling partners for further parameter studies.

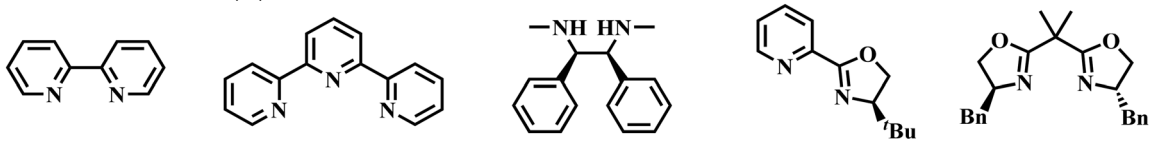
We next examined other ligands with the anhydride and alkyl bromides. The use of terpyridine (**L2**), *meso*-1,2-dipheny-

Table 1 Optimization of the reaction conditions[a]



1a 2 3 4 2a 2l

Entry	Nickel source	Solvent	1a : 2a	Zn (equiv.)	Conc. (M)	T (°C)	Ligand	Yield[b] (%) (3/4)
1	$Ni(COD)_2$	DMA	1 : 2	1.5	0.4	80	**L1**	22/0
2[c]	NiI_2	DMA	1 : 2	1.5	0.4	80	**L1**	16/0
3	$Ni(COD)_2$	DMF	1 : 2	1.5	0.4	80	**L1**	Trace
4[d]	$Ni(COD)_2$	DMSO	1 : 2	1.5	0.4	80	**L1**	Trace
5	$Ni(COD)_2$	DMA	1 : 1	1.5	0.4	80	**L1**	45/0
6	$Ni(COD)_2$	DMA	1.5 : 1	1.5	0.4	80	**L1**	52/0
7[e]	$Ni(COD)_2$	DMA	2 : 1	1.5	0.4	80	**L1**	43/0
8	$Ni(COD)_2$	DMA	1.5 : 1	2.0	0.4	80	**L1**	56/0
9[f]	$Ni(COD)_2$	DMA	1.5 : 1	3.0	0.4	80	**L1**	48/0
10	$Ni(COD)_2$	DMA	1.5 : 1	2.0	0.5	80	**L1**	58/0
11	$Ni(COD)_2$	DMA	1.5 : 1	2.0	1.0	80	**L1**	72/0
12	$Ni(COD)_2$	DMA	1.5 : 1	2.0	1.3	80	**L1**	78/0
13[g]	$Ni(COD)_2$	DMA	1.5 : 1	2.0	2.0	80	**L1**	66/0
14	$Ni(COD)_2$	DMA	1.5 : 1	2.0	1.3	80	**L2**	Trace/0
15	$Ni(COD)_2$	DMA	1.5 : 1	2.0	1.3	80	**L3**	Trace/0
16	$Ni(COD)_2$	DMA	1.5 : 1	2.0	1.3	80	**L4**	Trace/0
17[h]	$Ni(COD)_2$	DMA	1.5 : 1	2.0	1.3	80	**L5**	Trace/12
18[i]	$Ni(COD)_2$	DMA	1.5 : 1	2.0	1.3	80	**L5**	Trace/19
19[i,j]	$NiCl_2(PPh_3)_2$	DMA	1.5 : 1	2.0	1.3	80	**L5**	Trace/45
20[i,k]	$NiCl_2(PPh_3)_2$	DMA	1 : 2	2.0	1.3	80	**L5**	Trace/57
21[i,l]	$NiCl_2(PPh_3)_2$	DMA	1 : 2	2.0	1.3	100	**L5**	Trace/64
22[l,m]	$NiCl_2(PPh_3)_2$	DMA	1 : 2	2.0	1.3	100	**L5**	Trace/80
23	Without Ni, L, or Zn							0



L1 L2 L3 L4 L5

[a] Conditions: all of the experiments were performed with **1a**, **2a**, the nickel source and the ligand in a dry solvent with stirring for 12 h under a nitrogen atmosphere. [b] Isolated yields. [c] For details on nickel source screening for the synthesis of **3**, see Table S1. [d] For details on solvent screening, see Table S2. [e] For details on the ratio of starting materials screening for the synthesis of **3**, see Table S3. [f] For details on the amount of Zn powder screening, see Table S4. [g] For details on the concentration screening, see Table S5. [h] For details on ligand screening, see Table S7. [i] (2-Bromoethyl)benzene **2l** was used. [j] For details on nickel source screening for the synthesis of **4**, see Table S10. [k] For details on the ratio of starting materials screening for the synthesis of **4**, see Table S11. [l] For details on the temperature screening for the synthesis of **4**, see Table S12. [m] 20% mol $NiCl_2(PPh_3)_2$ was used for 24 h. DMA is *N*,*N*-dimethylacetamide, DMF is *N*,*N*-dimethylformamide, DMSO is dimethyl sulfoxide.

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lethane-1,2-diamine (**L3**) and pyrox ligand **L4** gave only trace amounts of β-keto acid **3aa** (Table 1, entries 14–16). The bisoxazoline (Box) ligand (**L5**) also gave a trace amount of **3aa** but generated the decarbonylative product with 12% isolated yield (Table 1, entry 17, for details on ligand screening, see Table S7). This result inspired us to search for a catalyst for the decarbonylation product. Upon investigation of an array of reaction parameters, the yield of **4ao** did not reach 25%. We next used primary alkyl bromide **2l** to optimize the reaction conditions and found that $Cl_2Ni(PPh_3)_2$ was more suitable for the decarbonylative cross-coupling reaction, giving **4al** in 45% isolated yield (Table 1, entry 19, for details on nickel source screening for the synthesis of **4al**, see Table S10). After extensive screening of reaction parameters, including the ratio of starting materials, temperature, catalyst loading and reaction time, the decarbonylative product **4al** was produced in 80% isolated yield (Table 1, entry 22). The lack of enantioselectivity was attributed to the high temperature of the reaction (100 °C). Lowering the reaction temperature gave reduced conversions (see Table S12). Control experiments revealed that nickel, ligand and Zn powder were all needed for the cross-coupling; leaving out any one of these components shut down the reaction (Table 1, entry 23). Ultimately, the optimized conditions for the synthesis of alkylated γ-keto acids were: 1.5 equiv. of anhydride **1a**, 1.0 equiv. of alkyl bromide **2a**, 2.0 equiv. of zinc powder, 10 mol% $Ni(COD)_2$ and 15 mol% bipy in DMA at 80 °C for 12 h (entry 12). The optimized conditions for the decarbonylative cross-coupling reaction are: 1.0 equiv. of **1a**, 2.0 equiv. of **2l**, 2.0 equiv. of zinc powder, 20 mol% $NiCl_2(PPh_3)_2$ and 30 mol% **L5** in DMA at 100 °C for 24 h (entry 22).

Determination of the scope in the synthesis of keto acids

With the optimized conditions in hand, we next tested the substrate scope of alkyl bromides in the synthesis of keto acids **3** (Fig. 3). In general, a diverse array of primary and secondary alkyl bromides were viable under the optimized conditions (Fig. 3, top). Both cyclic and acyclic secondary alkyl bromides, such as cyclohexyl and cyclopentyl bromide, 2-bromopropane, and 3-bromopentane, exhibited good to excellent reactivity,

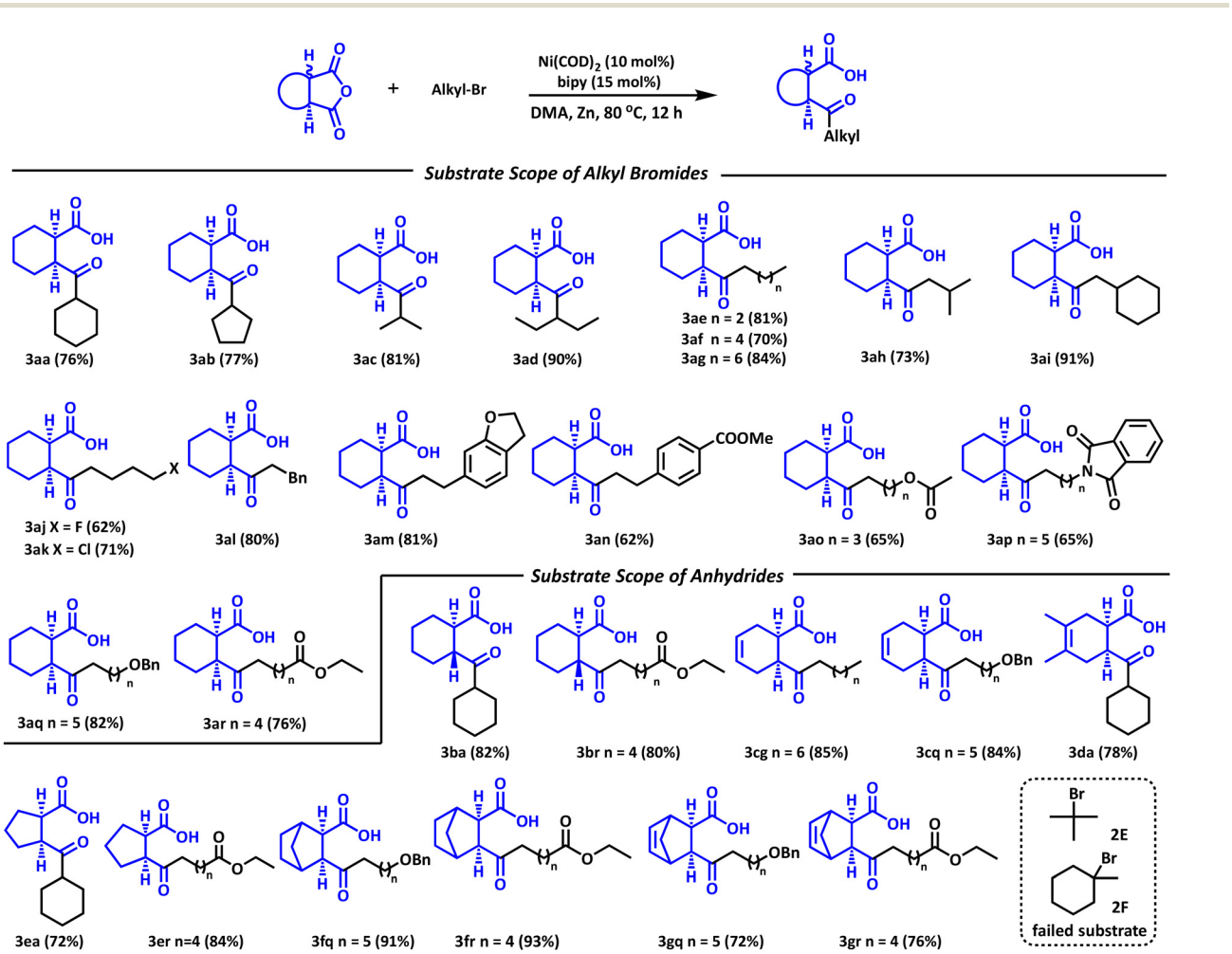

Fig. 3 Substrate scope of direct reductive cross-coupling of anhydrides and unactivated alkyl bromides. Reactions were performed on a 0.3 mmol scale with **1** (1.5 equiv.), **2** (1.0 equiv.), $Ni(COD)_2$ (10 mol%), bipy (15 mol%) and DMA (1.3 M) at 80 °C for 12 h.

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affording products **3aa–3ad** in 76–90% yields. Primary long-chain alkyl bromides underwent the transformation to give **3ae–3ag** in 70–84% yields. β-Branched alkyl bromides tend to undergo faster β-hydride elimination of the alkyl metal intermediates.[58–61] Fortunately, β-hydride elimination did not prove problematic with *sec*-Bu–Br or cyclohexyl methyl bromide, which furnished **3ah** and **3ai** in 73% and 91% yields, respectively. Excellent chemoselectivity was exhibited in the reaction with C(sp^3)–Br bonds over C(sp^3)–Cl and C(sp^3)–F containing substrates, as exemplified by the generation of fluoro- and chloro-containing products **3aj** and **3ak** in 62% and 71% yields, respectively. It is noteworthy that alkyl bromides bearing benzyl, benzodihydrofuran, ester, imide and ether functional groups smoothly coupled with **1a** to generate the corresponding products **3al–3ar** in 62–82% yields.

Next, we focused on the scope of bi- and tricyclic anhydride derivatives (Fig. 3, bottom). The *trans*-anhydride **1b** exhibited similar reactivity to the *cis*-diastereomer **1a**, furnishing **3ba** and **3br** in 82 and 80% yields, respectively, with full retention of the *trans*-stereochemistry. The utility of unsaturated anhydrides in our transformation, such as *cis*-cyclohexenedicarboxylic anhydride **1c** and its analogue bearing two methyl groups **1d**, was demonstrated by the generation of products **3cg**, **3cr**, and **3da** in 78–85% yields. Cyclopentyl succinic anhydride underwent this transformation with both secondary and primary alkyl bromides, giving functionalized *cis*-γ-keto acids in 72% (**3ea**) and 84% (**3er**) yields, respectively. Tricyclic anhydride **3f** was an excellent substrate under our reaction conditions, as exemplified by the generation of **3fq** and **3fr** in >90% yield. The unsaturated tricyclic anhydride led to the bicyclic products **3gq** and **3gr** in 72–76% yields. It should be noted that tertiary alkyl halides, such as *tert*-butyl bromide (**2E**) and 1-bromo-1-methylcyclohexane (**2F**), were also examined, but gave low yields.

Determination of the scope in the decarbonylative synthesis of acids

Next, we examined the substrate scope of decarbonylative reductive cross-coupling of anhydrides and alkyl bromides, as shown in Fig. 4. Simple primary long-chain alkyl bromides were good substrates for our reaction system, offering the corresponding decarbonylative products (**4aa–4ad**) with 80–86% isolated yields. The branched primary alkyl bromide **2t** provided the target product **4ae** in 69% yield. Primary alkyl bromides containing carbocycles, such as bromomethyl cyclopentane **2u** and bromomethyl cyclohexane **2i**, provided the cross-coupling products **4af** and **4ag** with 81% and 88% yields, respectively.

We next focused on functionalized alkyl bromides. It was found that alkyl bromides bearing ether and ester functional

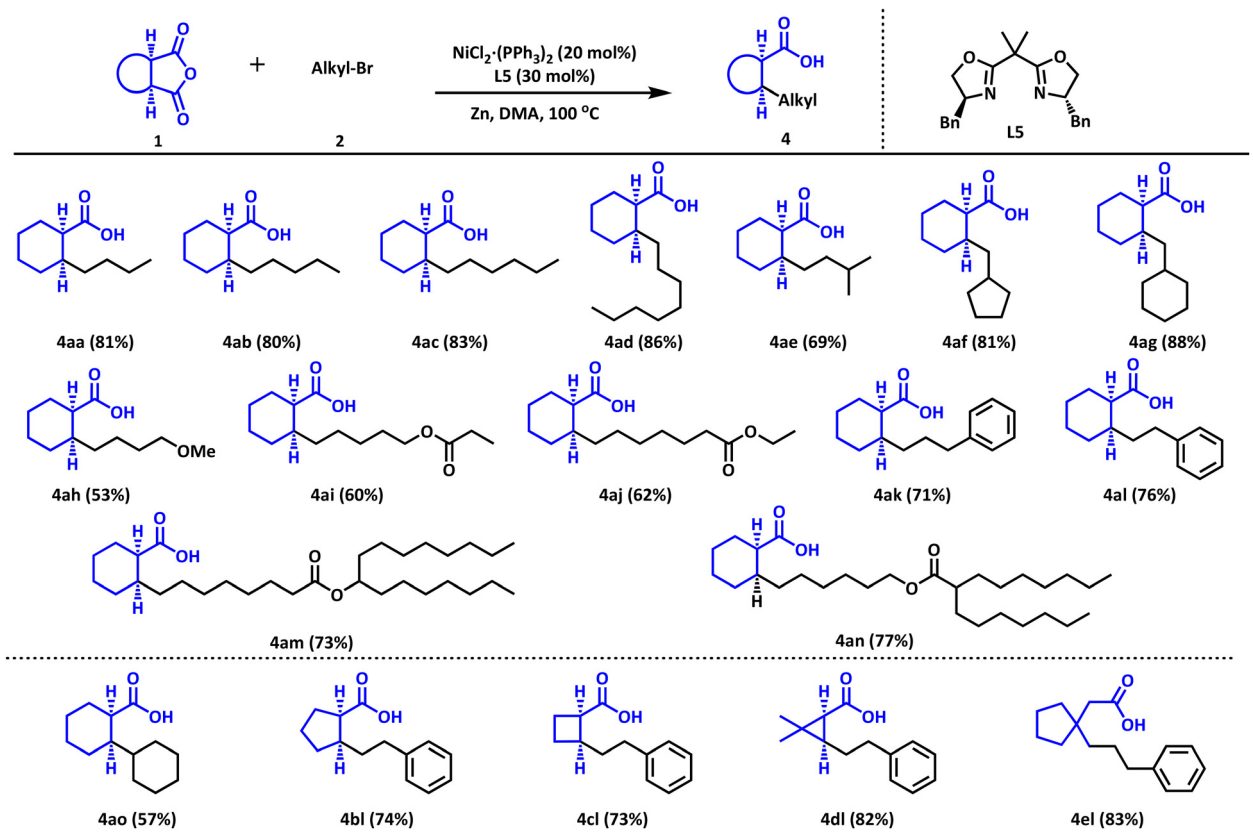

Fig. 4 Substrate scope of decarbonylative reductive cross-coupling of anhydrides and unactivated alkyl bromides. Reactions were performed on a 0.3 mmol scale with **1** (1.0 equiv.), **2** (2.0 equiv.), $NiCl_2(PPh_3)_2$ (20 mol%), **L5** (30 mol%) and DMA (1 M) at 100 °C for 24 h.

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groups smoothly coupled with **1a** to generate the corresponding products **4ah–4aj** in 53–62% yields. 1-Bromo-3-phenylpropane **2y** and (2-bromoethyl)benzene **2l** provided the target products **4ak** and **4al** in 71% and 76% yields, respectively. Given that certain long-chain lipid molecules can facilitate *m*RNA delivery,[62–64] two novel compounds **4am** (73%) and **4an** (77%) were synthesized by conjugating these lipids with anhydrides. Investigation of the secondary bromocyclohexane **2a** under decarbonylative cross-coupling conditions gave the coupling product **4ao** in 57% yield. Anhydrides containing five- (**1e**), four- (**1h**) and three-membered rings (**1i**) were viable coupling partners, producing acids **4bl–4dl** with 73–82% yields. 8-Oxaspiro[4.5]decane-7,9-dione provided the decarbonylative cross-coupling product **4el** with 83% isolated yield.

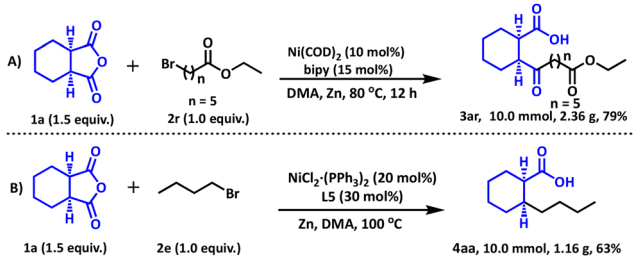

Fig. 5 Scale-up studies. (A) Scale-up of the reductive cross-coupling of anhydride **1a** and alkyl bromide **2r**. (B) Scale-up of the decarbonylative reductive cross-coupling of anhydride **1a** and *n*-butyl bromide **2e**.

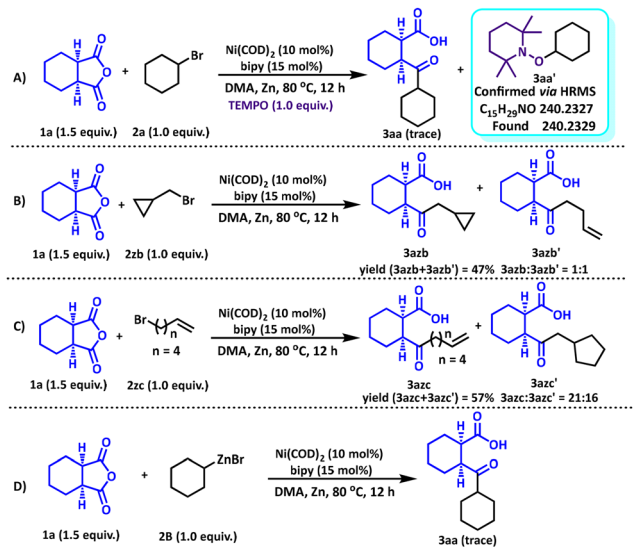

Fig. 6 Probing radical mechanisms. (A) Inhibition of the reaction in the presence of TEMPO. (B) Radical clock reaction leading to the ring-opened product **3azb′**. (C) Radical clock reaction leading to the ring-closed product **3azc′**. (D) Ruling out organozinc **2B** as a possible reaction intermediate.

10.0 mmol scale reactions

To test the scalability of the DCEC, alkyl bromide **2r** (10 mmol) bearing an ester was selected to couple with bicyclic anhydride **1a** (15 mmol) under the standard conditions. Product **3ar** was isolated in 79% yield (Fig. 5A). To further evaluate the utility of this decarbonylative cross-coupling reaction, 10 mmol of anhydride **1a** was coupled with 20 mmol of *n*-butyl bromide **2e** and the target product **4aa** was isolated with 63% yield (Fig. 5B).

Mechanistic studies of the generation of keto acids

To shed light on this cross-electrophile coupling reaction mechanism, a series of experiments were performed, as shown in Fig. 6. We speculated that an alkyl radical was present in our reaction system. The radical scavenger 2,2,6,6-tetramethylpiperidinooxy (TEMPO) was, therefore, added to the reaction under the standard conditions.[65,66] We found that the cross-coupling product **3aa** was formed in only trace amounts. On analyzing this reaction by HRMS, we observed that the alkyl radical was trapped by the radical scavenger TEMPO (Fig. 6A). To further probe for radicals in this transformation, radical clock studies[65,67,68] were performed (Fig. 6B). The *cis*-1,2-cyclohexanedicarboxylic anhydride **1a** was reacted with (bromomethyl)cyclopropane **2zb** and the cross-coupling product **3azb** was produced with the ring-opened product **3azb′** in a 1 : 1 ratio with a total yield of 47%. This result is consistent with the rearrangement process of a cyclopropyl-methyl radical to the homoallylic radical.[69] Moreover, 5-hexenyl bromide **2zc**, which upon generation of a primary radical can undergo cyclization, generated both the uncyclized and the ring-closed products **3azc** : **3azc′** in a 21 : 16 ratio in an overall yield of 57% (Fig. 6C). These observations led us to propose that the reaction proceeded *via* a single electron reduction of the alkyl bromide to generate the alkyl radical intermediate.

In order to explore the possibility of generation of alkyl zinc intermediates in the reaction, an *in situ* formed cyclohexylzinc bromide **2B** (1.0 M) was independently synthesized[70–72] and treated with the *cis*-1,2-cyclohexanedicarboxylic anhydride **1a** under the standard conditions (Fig. 6D). The cross-coupling product **3aa**, however, was not detected under these conditions, which suggests that the alkyl zinc intermediate is not an active species in this system. Taken together, the results from Fig. 6A–D support the notion that the cross-electrophile coupling reactions proceed *via* a SET process where the alkyl bromide generates an alkyl radical intermediate that is likely captured by nickel. Reductive elimination before decarbonylation results in C(sp^2)–C(sp^3) bond formation.

Mechanistic studies on the decarbonylative reaction of anhydrides

Next, we explored the mechanism of the decarbonylative reductive cross-coupling of anhydrides and alkyl bromides. A combination of $Ni(COD)_2$, **L1** and anhydride **1a** or of $Ni(COD)_2$, **L5** and anhydride **1a** (Fig. S5-A and S5-B) in THF was used. Upon mixing of the reagents at room temperature, the color of the solution changed to ruby red, and a precipitate was formed.

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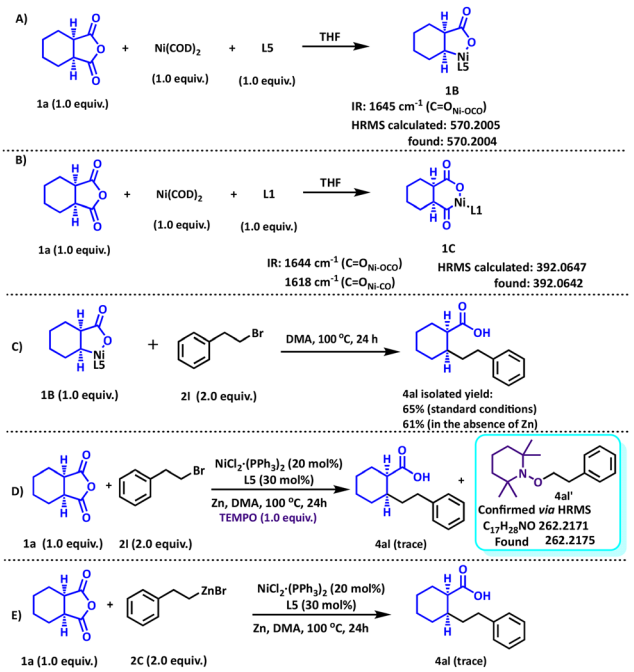

Fig. 7 Probing mechanisms in the decarbonylative reactions. (A and B) Examination of the reactions of anhydrides with (L)Ni^0. (C) Alkylation of the independently synthesized Ni homoenolate intermediate **1B**. (D) Inhibition of the reaction in the presence of TEMPO. (E) Examination of organozinc **2C** as a possible reaction intermediate.

Unfortunately, both intermediates exhibited poor solubility in the deuterated solvents examined and were not characterizable by NMR. As a result, infrared spectroscopy and HRMS were employed (Fig. S5–7). A comparison of the infrared spectra (Fig. S5B and C) revealed the following observations: (1) Ni(0) oxidatively added the anhydride with ligand **L1** and **L5** and (2) when ligand **L5** was used with Ni(COD)$_2$ and anhydride **1a**, only one carbonyl absorption was present in the IR spectrum (1645 cm^{-1}, C=O$_{Ni\text{-}OCO}$, Fig. 7A). In contrast, when ligand **L1** was used, two prominent carbonyl absorptions were observed at 1644 cm^{-1} (C=O$_{Ni\text{-}OCO}$) and 1618 cm^{-1} (C=O$_{Ni\text{-}CO}$) (Fig. 7B).[73–75] HRMS spectra of the adducts were acquired and found to be consistent with the proposed structures in Fig. 7A and B. Collectively, these experimental results support the notion that ligand **L5** promotes the decarbonylation process. Conversely, ligand **L1** disfavors decarbonylation. Here, it is worth noting that in our past studies with simple cyclic anhydrides, a Ni(**L1**)-based catalyst provided decarbonylative products under similar conditions.[48] Thus, we speculate that the decarbonylative/acylative manifolds are controlled by the anhydride oxidative addition intermediate and the ligand. In contrast to our results, the system of Sigman, Reisman and co-workers was proposed to be under alkyl halide substrate control, where the relative rate of radical generation was postulated to dictate the selectivity.[57]

To explore the relative reactivity of the alkyl bromide and anhydride with (L)Ni^0, we examined the addition of *cis*-1,2-cyclohexanedicarboxylic anhydride **1a** and (2-bromoethyl) benzene **2l** with 1.0 equiv. of Ni(COD)$_2$ and 1.0 equiv. of **L1** in THF at room temperature (Fig. 8A). The reactivities were determined based on the consumption of each starting material. We found that the *cis*-1,2-cyclohexanedicarboxylic anhydride **1a** was consumed much faster than (2-bromoethyl)benzene **2l**. No cross-coupling product was observed under these conditions by GC analysis, which was not surprising because the catalytic reactions were conducted at 100 °C. Notably, substitution of **L1** with **L5** also led to faster consumption of the anhydride (Fig. 8B). We also conducted the reaction using 1.0 equiv. of $NiCl_2(PPh_3)_2$, 1.0 equiv. of **L5** and 1.0 equiv. of Zn powder in THF at room temperature (Fig. 8C). It was found that the *cis*-1,2-cyclohexanedicarboxylic anhydride **1a** was again consumed much faster than (2-bromoethyl)benzene **2l**. These studies indicated that the cyclic anhydride undergoes oxidative addition faster than the alkyl bromide in the presence of stoichiometric amounts of Ni(COD)$_2$/**L1** or Ni(COD)$_2$/**L5** as well as $NiCl_2(PPh_3)_2$/**L5**/Zn powder.

To determine if Ni(I) might be reacting faster with the anhydride or alkyl halide, [(L)Ni^{I}Cl]$_2$ (2D, L = di-*t*-Bu-bipy) was independently synthesized (Fig. 8D).[76] The Ni(I) complex was reacted with *cis*-1,2-cyclohexanedicarboxylic anhydride (**1a**) and (2-bromoethyl)benzene (**2l**) in THF as performed above (Fig. 8E and F). It was observed that the alkyl bromide was consumed more rapidly than the anhydride at both room temperature and 40 °C, supporting the idea that (L)Ni^I promotes the generation of alkyl radicals from alkyl bromides even in the presence of reactive anhydrides.

On the basis of the experimental results presented above, and prior studies,[47,48,77–81] a plausible dual catalytic cycle for this chemoselective nickel-catalyzed cross-electrophile coupling of cyclic anhydrides with alkyl bromides is outlined in Fig. 9. A key study guiding our proposal was that of Yamamoto[82,83] and co-workers, who demonstrated that the reaction of (bipy)Ni^0(COD) with succinic anhydride was *second order* (first order in both Ni^0 and the anhydride). Based on this convincing report, we propose that the catalytic cycles in Paths 1 and 2 begin with (L)Ni^0(COD) undergoing loss of COD and oxidative addition of the anhydride to provide the (**L**)Ni^{II} species **A**. In Path 1 with ligand **L1**, reduction of **A** by $\frac{1}{2}$ Zn generates the acyl nickel(I) species **B**.[84–86] Activation of the alkyl bromide **2** by **B** generates an alkyl radical and Ni(II) intermediate **C**. Intermediate **C** and the alkyl radical combine *via* oxidative capture to form the (**L1**)Ni^{III} complex **D**.[87,88] Subsequent reductive elimination of **D** generates (**L1**)Ni^I and the zinc carboxylate **F**. The C(sp^2)–C(sp^3) coupling product is obtained after acidic workup (Fig. 9, Path 1).

When the bisoxazoline (Box) ligand **L5** is used, oxidative addition of the anhydride to Ni(0) to form Ni(II) complex **A** is followed by the loss of CO to give the C(sp^3)–Ni^{II} bound Ni-homoenolate intermediate **G**.[36] Reduction of the homoenolate by $\frac{1}{2}$ Zn powder generates nickel(I) species **H**. This intermediate undergoes single electron transfer to the alkyl bromide **2** with the formation of the alkyl radical. The newly formed radical is oxidatively captured by Ni(II) intermediate **I** to form the (**L5**)Ni^{III}-alkyl complex **J**. Reductive elimination of **J** leads to an (**L5**)

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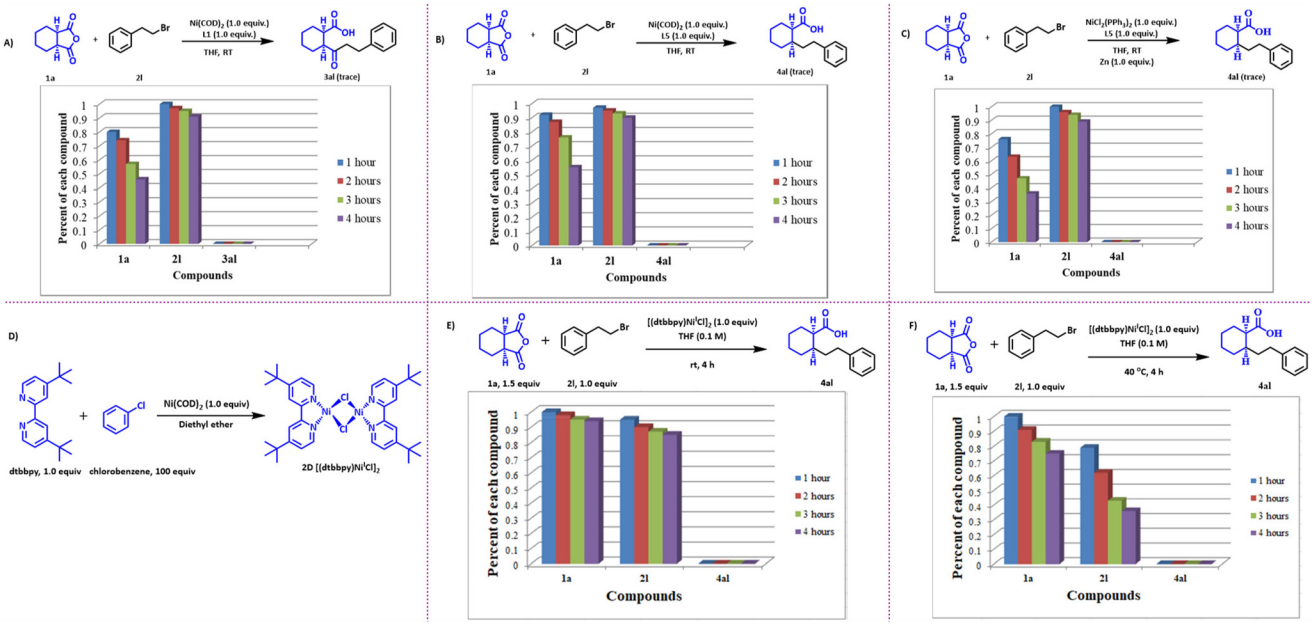

Fig. 8 Reactivity studies with Ni(0) and Ni(I). (A) Selectivity in oxidative addition to (L)Ni^0. Percent of remaining **1a** and **2l**. (B) Selectivity in oxidative addition to (L)Ni^0. Percent of remaining **1a** and **2l**. (C) Selectivity in oxidative addition to (L)Ni^{II}. Percent of remaining **1a** and **2l**. (D) Synthesis of [(dtbbpy)Ni^{I}Cl]$_2$. (E) Selectivity in oxidative addition to (L)Ni^{I}. Percent of remaining **1a** and **2l** at room temperature. (F) Selectivity in oxidative addition to (L)Ni^{I}. Percent of remaining **1a** and **2l** at 40 °C.

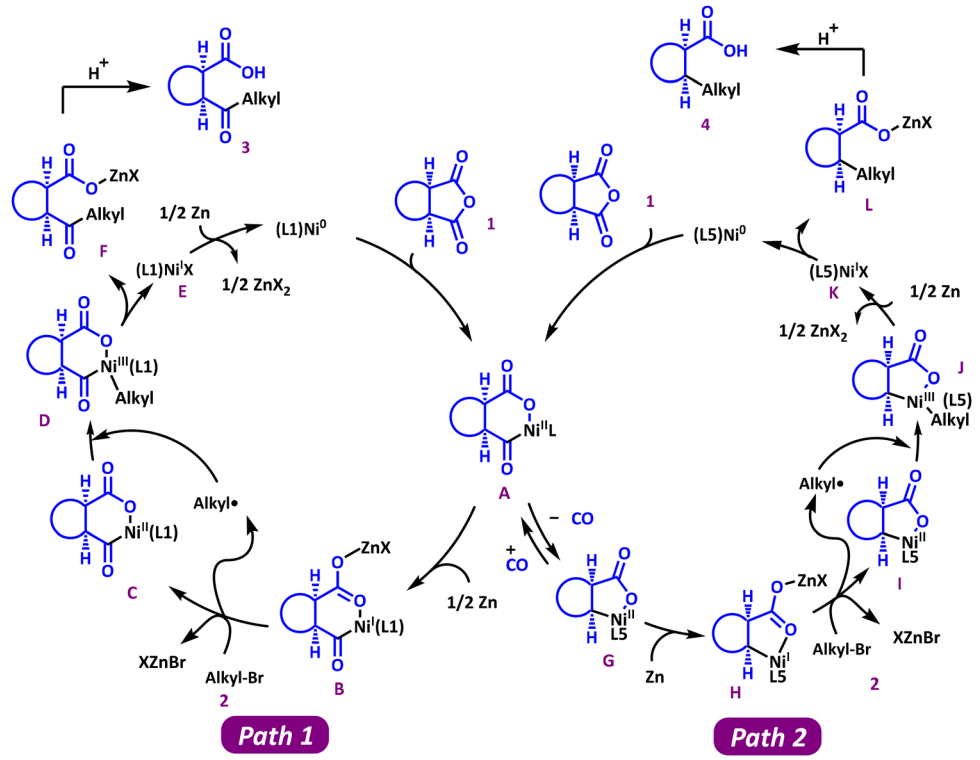

Fig. 9 Working mechanism proposal. Path 1: possible mechanism for **L1**-controlled nickel-catalyzed C(sp^2)–C(sp^3) cross-electrophile coupling of cyclic anhydrides with alkyl bromides. Path 2: possible mechanism for **L5**-controlled nickel-catalyzed C(sp^3)–C(sp^3) cross-electrophile coupling of cyclic anhydrides with alkyl bromides.

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Ni^{I} complex (**K**) and the zinc carboxylate **L**. Finally, the cross-coupling product is obtained after acidic workup (Fig. 9, Path 2). While the exact reason for the bifurcating reaction manifolds must await computational studies, a few possibilities can be considered. Clearly, the structure of the Ni-acyl carboxylate intermediate (**A**) plays a role in the relative rate of decarbonylation, based on the observation in our past studies that monocyclic anhydrides readily decarbonylate[48] with the (**L1**)Ni-based catalyst whereas the bicyclic anhydrides used in this study do not (Path 1). This suggests that the bulkier bicyclic acyl carboxylate **A** in this study undergoes deinsertion more slowly, because deinsertion of CO increases the coordination number and hence the congestion around the Ni intermediate when CO is bound. Thus, we propose that the reduction of the Ni-center in **A** is more rapid with the less electron-donating bipy ligand **L1**. This reduction may also be facilitated by the non-innocence of the bipy ligand.[89] In contrast, in the more sterically hindered **L5** system, reduction by Zn may be hindered because of the sterically bulky ligands and the absence of a redox active ligand. It is known that minor changes in the ligand structure often have a significant impact on catalysis and reaction outcomes.[90–93]

Conclusions

In summary, the use of anhydrides in reductive cross-coupling reactions provides access to different reaction manifolds to afford either γ-keto acids or acid products with excellent control over chemoselectivity. We have developed ligand-controlled chemoselective nickel-catalyzed cross-electrophile coupling of cyclic anhydrides with functionalized alkyl bromides. Using the strategy developed herein, a diverse array of functionalized γ-keto acid derivatives (29 examples, 62–93% yields) and decarbonylative β-alkylated acid derivatives (19 examples, 53–88% yields) were obtained. The methods developed herein complement the previous strategy reported by Rovis and co-workers *via* the use of bench-stable electrophiles instead of moisture-sensitive organozinc reagents.[94–100] Moreover, by leveraging ligand control, our system enables the synthesis of products with distinct chemoselectivities, thereby providing a complementary approach to the strategy of the Sigman and Reisman groups, which modulates selectivity *via* the relative rates of radical generation.[57] Preliminary mechanistic studies and prior literature reports lead us to favor the (L)Ni(0) catalyst that selectively reacts with bicyclic anhydrides over alkyl bromides to form six-membered nickelocyclic intermediates. This intermediate undergoes a CO deinsertion with loss of CO to form the key Ni-homoenolate intermediate. In addition, radical clock and related mechanistic studies indicate that these cross-electrophile coupling reactions proceed *via* a SET to alkyl bromides rather than *via* alkylzinc intermediates. Further studies using anhydrides and related starting materials as Ni-homoenolate precursors are ongoing in our group and will be reported in due course.

Author contributions

T. Z. L., P. J. W. and Jianyou Mao conceived the project, designed the experiments and supervised the work. Y. W. performed the Ni^{I} experimental work. J. L. J., Z. H. L., X. Y. G., and Junyu Ma performed the experimental work. M. J. W. prepared the ligand. Y. F. S., Z. F. W. and X. R. Y. collected and interpreted the data. T. Z. L., P. J. W. and Jianyou Mao wrote the paper with input from all authors. All authors discussed the results in detail and commented on the paper.

Conflicts of interest

There are no conflicts to declare.

Data availability

All data related to the findings of this article are available in the supplementary information (SI).

Supplementary information: synthetic procedures and details on NMR spectra. See DOI: **https://doi.org/10.1039/d6qo00409a**.

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