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Manganese-Catalyzed [3 + 2] Cyclization of Ketones and Isocyanates via Inert C−H Activation

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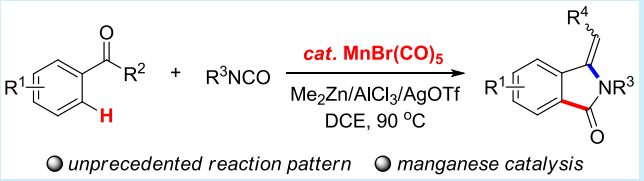
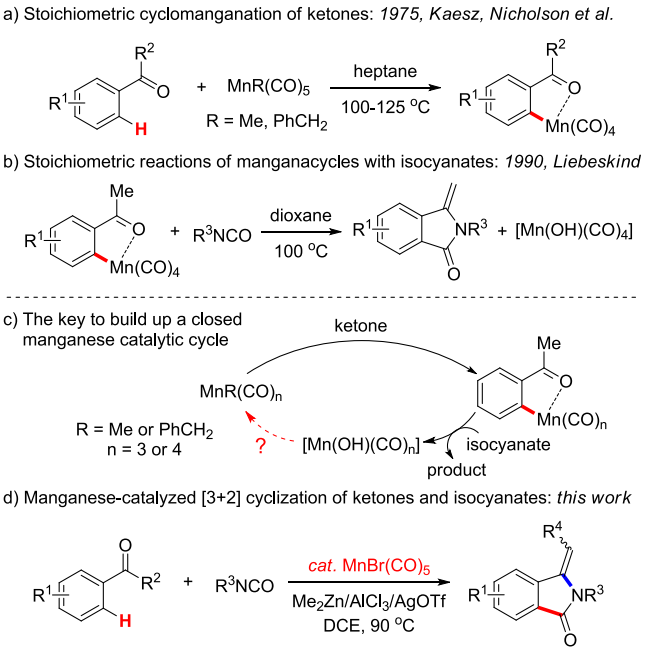
ABSTRACT: Stoichiometric cyclomanganation of aromatic ketones and further reactions of the thus-formed manganacycles with isocyanates were first reported by Kaesz and Liebeskind in 1975 and 1990, respectively. The buildup of a closed manganese catalytic cycle for the reaction of ketones and isocyanates remains an unsolved problem. Herein, an unprecedented trio of Me_2Zn/$AlCl_3$/AgOTf is developed to build up manganese catalysis, which enables the [3 + 2] cyclization of ketones with isocyanates via inert C−H activation to access 3-alkylidene phthalimidines in a straightforward manner unachieved by other transition metal catalyses.



Ketones are widely found in various bioactive molecules and functional materials. Meanwhile, as versatile synthetic intermediates, ketones can be readily converted into a wide range of functional molecules in organic synthesis. The strategy of inert C−H activation has spurred emerging unconventional reactivity and transformations of ketones, in which catalysis by 4d and 5d transition metals (Ru, Rh, Pd, etc.) has advanced rapidly in the last few decades.[1] In contrast, earth-abundant manganese catalysis has largely lagged behind in the inert C−H activation chemistry of ketones.[2,3] In 1975, Kaesz first reported the cyclomanganation reaction of aromatic ketones with methyl pentacarbonyl manganese [$MnMe(CO)_5$] to give the corresponding ketone-derived manganacycles (Scheme 1a).[4a] Afterward, Nicholson, Main, and Woodgate used less volatile [$Mn(CH_2Ph)(CO)_5$] to prepare the same type of manganacycles.[4b,c] Benefiting from the above reliable synthesis of ketone-derived manganacycles, a number of groups thereafter studied the stoichiometric reactions of these manganacycles with various reaction partners.[2a] Among them, Liebeskind disclosed the pioneering reaction of ketone-derived manganacycles with isocyanates to afford 3-alkylidene phthalimidines at 100 °C (Scheme 1b).[5] Though elegant, catalytic versions of these manganese-promoted reactions of ketones with isocyanates have remained unknown to date. We surmise that, in principle, [$Mn(OH)(CO)_4$] might be formed in Liebeskind's reaction, and how to regenerate [$MnR(CO)_n$] (R = Me, $PhCH_2$) from [$Mn(OH)(CO)_n$] will be the key to build up a closed manganese catalytic cycle for the reaction of ketones and isocyanates (Scheme 1c). The compatibility and efficiency of these combinative steps in a catalytic cycle are vital to the success of the expected manganese catalysis. To address this issue, we herein disclose a Me_2Zn/$AlCl_3$/AgOTf trio that enables the manganese-catalyzed [3 + 2] cyclization of ketones and isocyanates via inert C−H activation to approach varied 3-alkylidene phthalimidines directly (Scheme 1d).[6]

Scheme 1. Manganese-Promoted Stoichiometric and Catalytic Reactions of Ketones and Isocyanates



At the outset, we chose *p*-methoxyacetophenone (**1a**) and *p*-tolyl isocyanate (**2a**) as model substrates to screen the reaction

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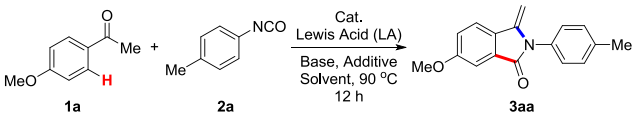
Table 1. Optimization of the Reaction Parameters[a]



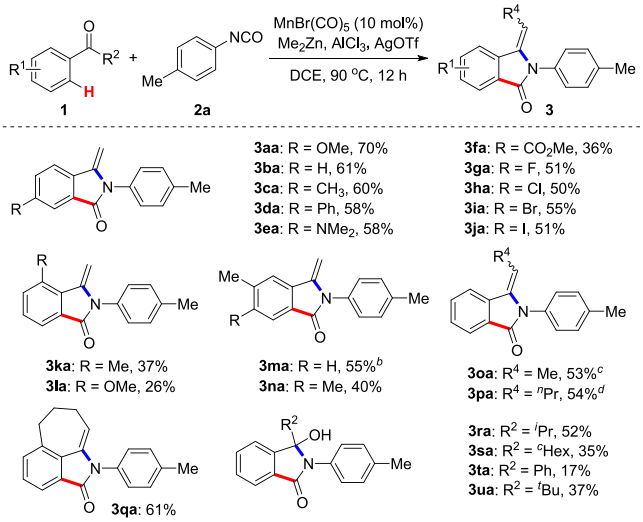
entry	cat.	LA	additive	base	solvent	yield (%)[b]
1	$MnBr(CO)_5$	$ZnBr_2$	–[c]	Me_2Zn	DCE	5
2	$MnBr(CO)_5$	$CuCl_2$	–[c]	Me_2Zn	DCE	13
3	$MnBr(CO)_5$	$Cu(OAc)_2$	–[c]	Me_2Zn	DCE	14
4	$MnBr(CO)_5$	$FeCl_3$	–[c]	Me_2Zn	DCE	13
5	$MnBr(CO)_5$	$AlCl_3$	–[c]	Me_2Zn	DCE	33
6	$MnBr(CO)_5$	–[d]	–[c]	Me_2Zn	DCE	0
7	$MnBr(CO)_5$	$AlCl_3$	–[c]	Me_2Zn	DME	4
8	$MnBr(CO)_5$	$AlCl_3$	–[c]	Me_2Zn	^{t}BuOMe	30
9	$MnBr(CO)_5$	$AlCl_3$	–[c]	Me_2Zn	toluene	15
10	$MnBr(CO)_5$	$AlCl_3$	–[c]	Me_2Zn	dioxane	16
11[e]	$MnBr(CO)_5$	$AlCl_3$	–[c]	Me_2Zn	DCE[f]	50
12[e]	$MnBr(CO)_5$	$AlCl_3$	–[c]	Et_2Zn	DCE[f]	8
13[e]	$MnBr(CO)_5$	$AlCl_3$	–[c]	MeMgBr	DCE[f]	0
14[e]	$MnBr(CO)_5$	$AlCl_3$	–[c]	–[g]	DCE[f]	0
15[e]	$Mn_2(CO)_{10}$	$AlCl_3$	–[c]	Me_2Zn	DCE[f]	8
16[e]	–[h]	$AlCl_3$	–[c]	Me_2Zn	DCE[f]	0
17[i]	$MnBr(CO)_5$	$AlCl_3$	AgOTf	Me_2Zn	DCE[f]	71 (70)[j]

[a]Reaction conditions unless otherwise noted: **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst (0.02 mmol), Lewis acid (0.2 mmol), base (0.36 mmol), additive (0.04 mmol), solvent (1.0 mL), 90 °C, 12 h under a N_2 atmosphere. [b]Determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [c]No additive. [d]No Lewis acid. [e]**1a**:**2a** = 3:1. [f]DCE (2.0 mL). [g]No base. [h]No catalyst. [i]**1a**:**2a** = 2.5:1. [j]Isolated yield on a 0.5 mmol scale.

parameters (Table 1). We have recently developed manganese-catalyzed aromatic C–H transformations with unsaturated molecules by the aid of Me_2Zn and Lewis acids.[7] Therefore, the original $Me_2Zn/ZnBr_2$ system with $MnBr(CO)_5$ (10 mol %) in 1,2-dichloroethane (DCE) at 90 °C was first tested in the current reaction, but unfortunately, only a 5% NMR yield of the desired product **3aa** was detected (entry 1). A series of Lewis acids were then examined in order to render manganese catalytic in the reaction and further enhance the catalytic efficiency (entries 2–5).[8] To our delight, product **3aa** was formed in 33% NMR yield when $AlCl_3$ was employed as a Lewis acid (entry 5). Of note, no formation of **3aa** was found in the absence of a Lewis acid (entry 6). Variation of the reaction solvent showed that DCE was the most effective one (entries 7–10). Further changing the substrate ratio and the reaction concentration led to an improved yield of **3aa** (entry 11). The use of Et_2Zn or MeMgBr instead of Me_2Zn gave only inferior results (entries 12 and 13), and no reaction occurred without the base (entry 14). $Mn_2(CO)_{10}$ was much less effective than $MnBr(CO)_5$ as the catalyst (entry 15), and the reaction failed completely in the absence of catalyst (entry 16). Fortunately, product **3aa** was eventually obtained in 71% NMR yield and 70% isolated yield when a catalytic amount of AgOTf was added to the reaction mixture (entry 17).[8,9]

With the optimized conditions in hand, the scope of ketones was first explored with **2a** as a model reaction partner. As shown in Scheme 2, acetophenone derivatives bearing varied electron-donating and -withdrawing substituents at the *para* position of the phenyl ring were amenable to this protocol, smoothly affording the corresponding 3-alkylidene phthalimidines (**3aa**–**ja**). Moreover, it turned out that electron-rich groups were more beneficial to the reaction than electron-deficient ones. Of note, halogen groups (F, Cl, Br, and I) remained intact after the reaction (**3ga**–**ja**), allowing for

Scheme 2. Scope of Ketones[a]



[a]Reaction conditions: **1** (1.5 mmol), **2a** (0.5 mmol), $MnBr(CO)_5$ (0.05 mmol), $AlCl_3$ (0.5 mmol), AgOTf (0.1 mmol), Me_2Zn (0.9 mmol), DCE (5.0 mL), 90 °C, 12 h under a N_2 atmosphere. [b]Two regioisomers, **3ma**:**3ma′** = 10:1; the major regioisomer **3ma** is shown. [c]*E*/*Z* = 1.4:1. [d]*E*/*Z* = 1.5:1, two separable isomers: (*E*)-**3pa**, 32%; (*Z*)-**3pa**, 22%.

further synthetic elaborations of the products. Substituents at the *ortho* positions of the acetophenone, such as methyl and methoxy, had an obvious influence on the yields of the products (**3ka** and **3la**), presumably due to the enhanced steric hindrance. When *meta*-substituted acetophenones were adopted in the reaction, the cyclization preferred to occur at the less sterically hindered position with high to excellent regioselectivity (**3ma** and **3na**). Alkyl phenyl ketones such as

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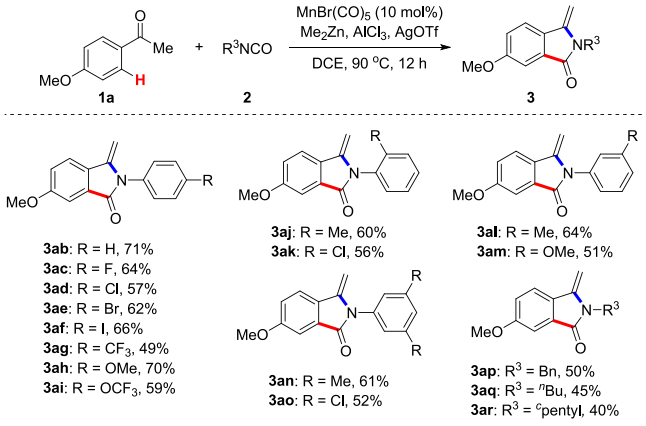
propiophenone and valerophenone bearing longer carbon chains reacted with **2a** to give *Z*- and *E*-configured products in synthetically useful yields with moderate *E*/*Z* ratios (**3oa** and **3pa**). The configuration of the C=C bond in these products might be determined by the steric hindrance between the R^4 group and the *p*-tolyl group. A bicyclic ketone was also applicable to this reaction, successfully leading to a tricyclic product (**3qa**). Interestingly, when isobutyrophenone, benzoylcyclohexane, benzophenone, and 2,2,2-trimethylacetophenone were subjected to the reaction conditions, 3-hydroxy-substituted isoindolin-1-ones (**3ra**–**ua**) were obtained without the formation of 3-alkylidene phthalimidines, presumably because of the steric hindrance of elimination or the absence of an adjacent hydrogen.

Next, various isocyanates were tested with **1a** under the standard reaction conditions (Scheme 3). Electronically varied

Scheme 3. Scope of Isocyanates[a]

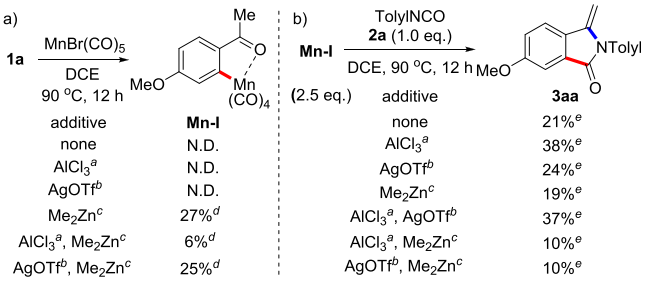


[a]Reaction conditions: **1a** (1.25 mmol), **2** (0.5 mmol), $MnBr(CO)_5$ (0.05 mmol), $AlCl_3$ (0.5 mmol), AgOTf (0.1 mmol), Me_2Zn (0.9 mmol), DCE (5.0 mL), 90 °C, 12 h under a N_2 atmosphere.

substituents on the benzene ring of the isocyanate were well-tolerated, and the expected products (**3ab**–**ai**) were obtained in 49–71% isolated yield. Reactions of ketone **1a** with *ortho*-substituted phenyl isocyanates also proceeded with ease (**3aj** and **3ak**), indicating that the increased steric hindrance did not affect the reaction too much. Meanwhile, *meta*-substituted isocyanates proved to be feasible starting materials, giving the corresponding products (**3al**–**ao**) smoothly. Besides aromatic isocyanates, benzyl isocyanate could also be applied to this protocol successfully (**3ap**). Finally, other aliphatic isocyanates such as *n*-butyl and cyclopentyl ones delivered the desired products **3aq** and **3ar** in moderate yields.

To probe the possible reaction pathways, a series of mechanistic experiments were carried out. Initially, a five-membered manganacycle **Mn-I** was obtained from **1a** and $MnBr(CO)_5$ in the presence of Me_2Zn at 90 °C in DCE, while $AlCl_3$ and/or AgOTf exhibited no positive effects on this cyclomanganation step (Scheme 4a). Then the stoichiometric reaction of **Mn-I** with **2a** was examined, and product **3aa** was obtained in 21% NMR yield (Scheme 4b), which echoed the previous results in Liebeskind's work.[5] Upon the addition of $AlCl_3$, the yield of **3aa** increased to 38%, indicating that $AlCl_3$ might act as a Lewis acid to activate the isocyanate. Of note, the presence of Me_2Zn or AgOTf had no obvious influence on the reaction outcome. Further combinations of these additives gave no better results.

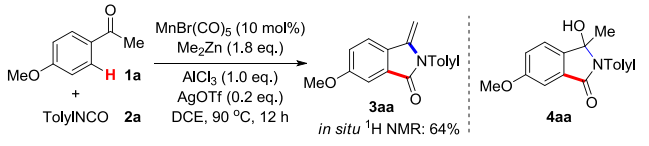
Scheme 4. Stoichiometric Mechanistic Experiments



[a]1.0 equiv. [b]0.2 equiv. [c]1.8 equiv. [d]Isolated yield. [e]^{1}H NMR yield. N.D. = not detected.

In order to figure out whether 3-alkylidene phthalimidine products like **3aa** were formed in situ or through dehydration of the alcohol intermediates such as **4aa** during the workup procedure, the reaction of ketone **1a** and isocyanate **2a** was conducted, and in situ ^{1}H NMR analysis of the crude reaction mixture was performed without quenching (Scheme 5). It

Scheme 5. In Situ ^{1}H NMR Analysis of the Crude Reaction Mixture

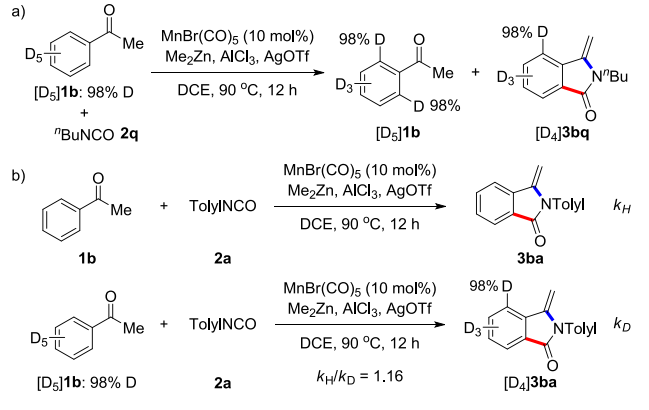


turned out that **3aa** was formed in 64% NMR yield, which is comparable to the yield obtained after workup (Table 1, entry 17), thus ruling out the pathway of dehydration of alcohol intermediate **4aa**.

Finally, deuterium-labeling experiments were examined to gain more insight into the C–H activation step. When pentadeuterated acetophenone ([D_5]**1b**) was reacted with *n*-butyl isocyanate (**2q**) under the standard reaction conditions, no H/D scrambling was detected on the benzene ring in both the substrate [D_5]**1b** and the product [D_4]**3bq** (Scheme 6a). Moreover, a kinetic isotope effect value of 1.16 was measured from two parallel reactions of **1b** and [D_5]**1b** with **2q** (Scheme 6b), suggesting that C–H bond activation was not involved in the turnover-limiting step.[10]

On the basis of the above mechanistic results and previous studies,[4,5,7] a plausible reaction mechanism is proposed in

Scheme 6. Deuterium-Labeling Experiments



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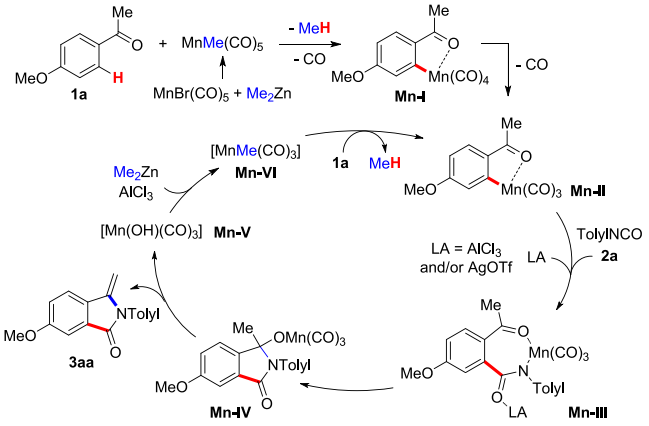
Scheme 7. $MnBr(CO)_5$ first reacts with Me_2Zn to give $MnMe(CO)_5$, which enables the cyclomanganation of ketone

Scheme 7. Tentative Reaction Mechanism



1a to afford manganacycle **Mn-I**. Dissociation of a CO ligand from **Mn-I** gives rise to **Mn-II**, the active species in the catalytic cycle. Subsequent insertion of isocyanate **2a** into the Mn−C bond of **Mn-II** leads to seven-membered manganacycle **Mn-III**. An intramolecular *N*-nucleophilic attack on the ketone occurs to deliver **Mn-IV**, which undergoes elimination to generate species **Mn-V** and release the product **3aa**. Of note, **Mn-V** might also exist in the form of higher-order manganese clusters, which are inactive for the reaction.[3x,8] Transmetalation of **Mn-V** with Me_2Zn in the presence of $AlCl_3$ then gives methylmanganese species **Mn-VI**, which then facilitates the C−H activation of ketone **1a** to regenerate **Mn-II**, thus closing the catalytic cycle of manganese.

In conclusion, we have achieved manganese catalysis to enable the [3 + 2] cyclization of ketones and isocyanates via inert C−H activation. On the basis of Kaesz's cyclomanganation of ketones and Liebeskind's stoichiometric reaction of manganacycles with isocyanates, the development of the $Me_2Zn/AlCl_3/AgOTf$ trio built up the unprecedented catalytic cycle of manganese in this transformation. Thus, a series of 3-alkylidene phthalimidines were synthesized directly from readily available ketones and isocyanates. Further explorations of manganese-catalyzed novel reactions of ketones via inert C−H activation are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00857.

Detailed experimental procedures, characterization data, and copies of ^1H NMR and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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