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COMMUNICATION

Mn(I)-Catalyzed Nucleophilic Addition/Ring Expansion via C-H Activation and C-C Cleavage

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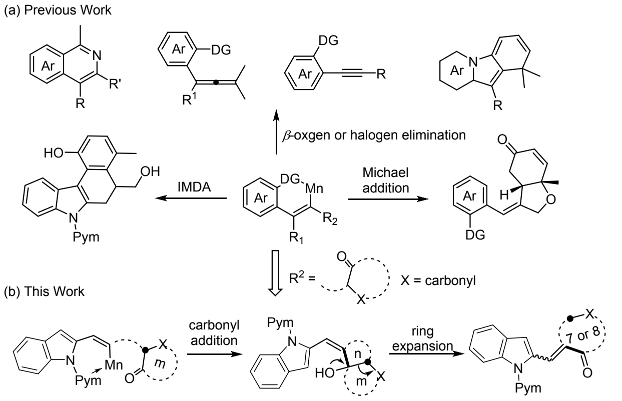
Mn(I)-catalyzed synthesis of Seven- or eight-membered carbocycles is disclosed via C-H activation of heteroarenes and coupling with alkyne-functionalized 1,3-cyclopentadiones or 1,3-cyclohexadiones. This n to n+2 (n = 5, 6) ring expansion reaction proceeded via a C-H alkenylation/carbonyl addition/retro-Aldol cascade. Structurally diverse mid-sized carbocycles were constructed via cleavage of both C-H and C-C bonds in a single operation.

Annulation reactions via catalytic C-H bond activation proved highly attractive in synthesis of complex cyclic products owing to high atom-economy and synthetic flexibility. However, only very limited examples have been reported for synthesis of 7- and 8-membered rings by following this strategy, and most of them rely on noble metal catalysis.[1] Furthermore, construction of cyclic products has also been mostly limited to simple annulation reactions, while complexity induced by skeleton rearrangement has been rarely attained.[2]

The high activity and low cost of manganese(I) catalysts have manefested unique significance in arene C-H activation.[3] A variety of C-H transformations have been realized via Mn(I) catalysis.[4-15] Among these systems, generation and transformations of a polarized Mn(I)-aryl species represent the key steps. Insertion of alkyne into a Mn-C(aryl) species produces a Mn(I)-alkenyl intermediate. As given in Scheme 1, besides being terminated by electrophiles, this species may undergo *β*- halogen and oxygen elimination to give allenes[11a,b] and alkynes.[5] Furthermore, rich transformations of these elimination products may occur *in situ* to deliver various heterocycles and fused rings. [11f,g]



Scheme 1. Transformations via Mn(I)-catalyzed C-H alkenylation. IMDA = Intramolecular Diels-Alder reaction.

Although the polarized Mn(I)-aryl bonds show reactivity towards alkyes,[11] carbonyl groups,[9,12] nitriles,[12] acrylate,[13a,b] enones,[14] and imines,[15] addition of Mn(I)-alkenyl species to electrophile is still limited, which may streamline construction of complex cyclic structures. We reasoned that the desired C-H alkenylation-nucleophilic addition may be attained using alkyne-tethered diketones as bifunctional coupling reagents.[16] By taking advantage of unique properties of the Mn-C species, our objective was to realize synthesis of hard-to-access 7- or 8-membered ring skeletons via a ring expansion process with cleavage of both C-H and C-C bonds in a single operation (Scheme 2).[17] Significantly, these kinds of rings are commonly encountered in natural products and pharmaceuticals.[18]

Some challenges exist in our design (Scheme 2). (1) The regioselectivity of alkyne insertion should be well-controlled to the 2,1-insertion to avoid formation of stable five-membered ring products (**C'**). (2) The competing protonolysis of the Mn-C(alkenyl) should be circumvented. (3) Formation of the desired intermediate **C** may carry a high energy barrier given expansion reaction leading to construction of seven- and even eight-membered rings via a cascade that merges C-H alkenylation with carbonyl addition/retro-Aldol reations by taking advantage of the high nucleophilicity of an alkenyl-Mn(I) bond. We initially examined the feasibility of the C-H alkyne

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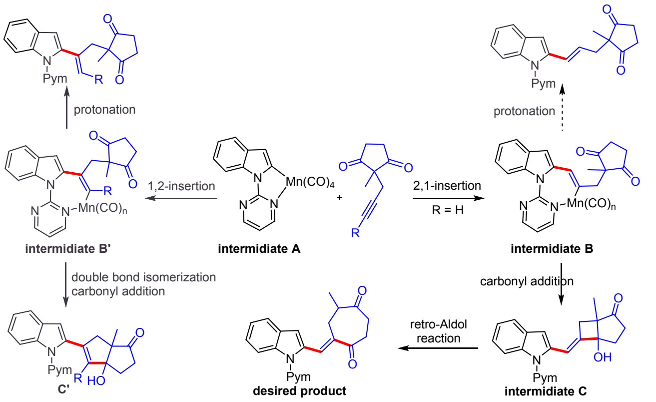
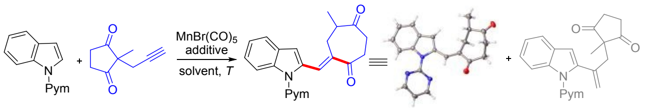


Scheme 2. Challenges in our reaction design.

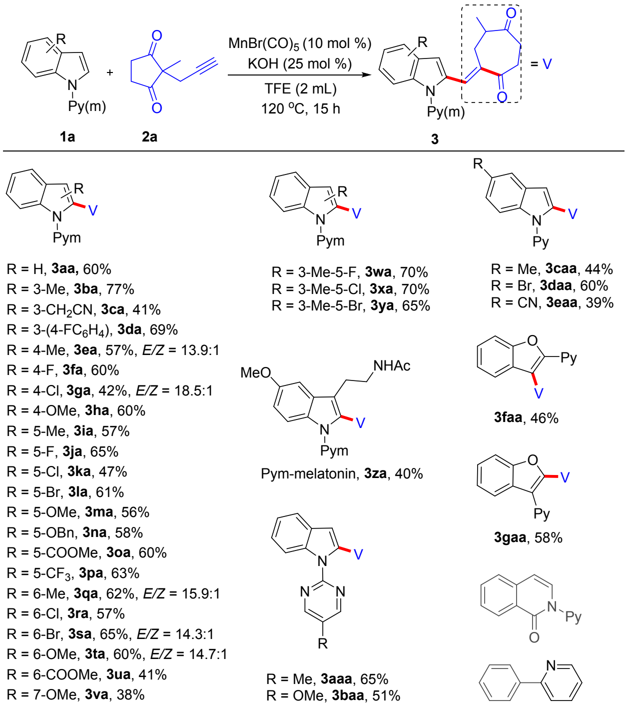
insertion/carbonyl addition/retro Aldol cascade in the coupling of *N*-pyrimidylindole (**1a**) and 2-methyl-2-(prop-2-yn-1-yl)cyclopentane-1,3-dione (**2a**, Table 1). To our delight, the reaction afforded a seven-membered carbocycle **3aa** in 23% yield (Table 1, entry 1). The *E* geometry of the exocyclic double bond was confirmed by X-ray crystallography (CCDC 1904663). The reaction efficiency was poor when DCE, 1,4-dioxane, toluene, or MeOH was used as the solvent (entries 2-5). Introduction of a base or Lewis acid generally gave better results (entries 6-10 and 13-14). Among them, KOH gave a moderate yield of **3aa** together with a hydroarylation by-product **4aa** (entry 11). Further screening revealed that the formation of **4aa** cannot be fully supressed (entry 12 and 15). Control experiment revealed that manganese was necessary for this transformation (entry 16). Finally, the conditions in entry 11 were chosen as the optimal conditions.

Table 1. Optimization of reaction conditions.[a,b]



entry	solvent (mL)	additive (mol %)	yield (%)
1	TFE (1)	-	23
2	DCE (1)	-	trace
3	dioxane (1)	-	n.d.
4	toluene (1)	-	n.d.
5	MeOH (1)	-	trace
6	TFE (1)	NaOAc (25)	25
7	TFE (1)	Cy_2NH (25)	43
8	TFE (1)	BPh_3 (25)	30
9	TFE (1)	DIPEA (25)	40
10	TFE (1)	KOH (25)	45 (15)
11	TFE (2)	KOH (25)	60 (22)
12[c]	TFE (2)	KOH (25)	52 (18)
13	TFE (2)	LiOH (25)	47
14	TFE (2)	NaOH (25)	40
15	TFE (2)	KOH (50)	60 (23)
16[d]	TFE (2)	KOH (25)	-

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $MnBr(CO)_5$ (10 mol%), additive (25 mol%), solvent, 120 °C, 15 h, under Ar, TFE = 2,2,2-trifluoroethanol. [b] Isolated yield of **3aa**, yield of **4aa** in parentheses, trace of **4aa** or not detected for other entries. [c] 110 °C. [d] no Mn catalyst.



Scheme 3. Scope of arenes. Standard conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $MnBr(CO)_5$ (10 mol%), KOH (25 mol%), TFE (2 mL), 120 °C, 15 h, under Ar, isolated yield.

With the optimal conditions in hand, the generality of this catalytic system was then explored. The scope was found to be broad with good compatibility of substituted indoles and several other heteroarenes (Scheme 3). Substituents such as alkyl (**1a**, **1b**, **1e**, **1i**, **1q**), aryl (**1d**), halides (**1f**, **1g**, **1j**-**1l**, **1r** and **1s**), alkoxyl (**1h**, **1m**, **1n** and **1t**), ester (**1o** and **1u**), and CF3 (1p) at the C3-, C4-, C5-, or C6-positions of N-pyrimidylindoles were tolerated regardless of the electronic nature, delivering the desired products in moderate to good yields (**3ba**-**3ua**). The indole with a C(7) OMe group only coupled with low efficiency (**3va**), indicative of sensitivity to steric effect. Multi-substituted indoles (**1w**-**1z**) also coupled smoothly with **2a** to afford the corresponding products. Using substituted pyrimidyl (**1aa** and **1ba**) or pyridyl (**1ca**-**1ea**) as the directing group did not affect the reaction efficiency. The cascade reaction was not limited to indole substrates. Electron-rich heteroarenes such as benzofurans gave positive results (**3faa** and **3gaa**). However, other arenes such as 2-phenylpyridine and 2-pyridinylisoquinolinone failed to give any reactivity in this catalytic system.

The compatibility of propargyl-substituted cyclic-ketones was next investigated (Scheme 4). It was found that introduction of different alkyl substituents at the α-position of carbonyl group (**2a**-**2e**) was tolerated. All the corresponding seven-membered

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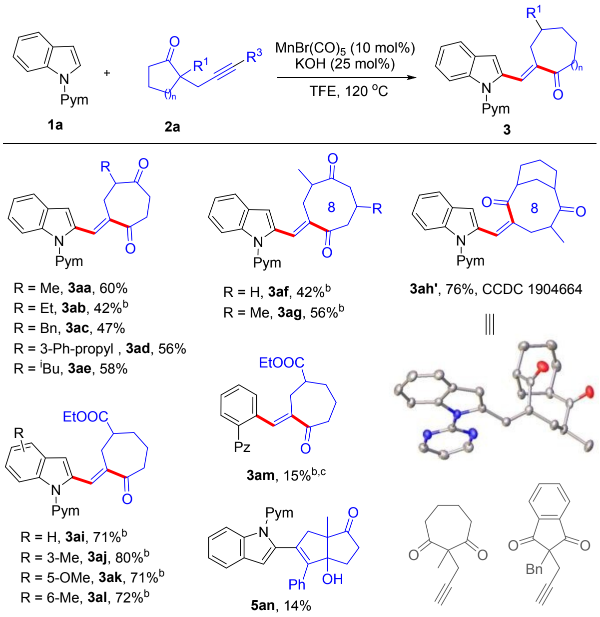
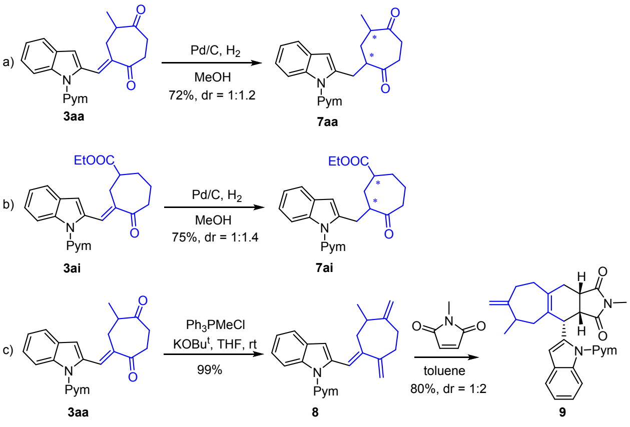


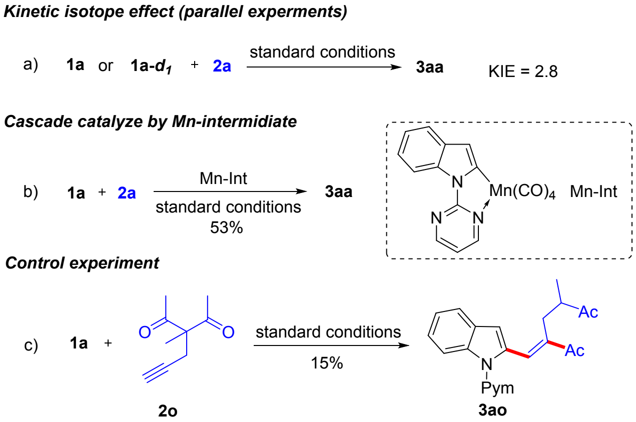
Scheme 4. Scope of β-dicarbonyl substrates.^{a} ^{a}Standard conditions, isolated yield. ^{b} Conditions B: Cy_2NH instead of KOH, DCM/TFE (1.5 mL/0.5 mL), 100 °C. ^{c} Pz = 1-Pyrazolyl.

rings were obtained in moderate yields (**3aa**-**3ae**, 42-60%). As expected, reaction of the corresponding 1,3-cyclohexadione afforded the desired eight-membered carbocycles (**3af** and **3ag**). Of note, a bridged mid-sized ring **3ah'** with Z geometry of the exocyclic double bond (CCDC 1904664) was obtained by using the corresponding bridged 1,3-dione **2h**. The difference of the geometry may be caused by the steric effect of the bridged bicyclic substrate. The coupling partner was not limited to cyclic diketones. When an ester group was introduced as an EWG to the *β*-position of the carbonyl group, the reaction proceeded smoothly (**3ai**-**3al**). Encouraged by this result, a less electron-rich phenylpyrazole was examined, and low yield was obtained (15%, **3am**). In contrast, 1,3-cycloheptadione and benzocyclopentanedione failed as substrates for the system. Extension of the alkyne to internal ones met with difficulty. Still, a phenyl-terminated alkyne substrate **2n** underwent coupling with **1a** to give a fused ring **5an** in poor yield, as a result of 1,2-insertion process.[12]



Scheme 5. Product derivatization.

To demonstrate the synthetic utilities of the seven-membered carbocycles, hydrogenation of both **3aa** and **3ai** was performed, delivering products **7aa** and **7ai** in good yields and 1:1.2-1.4 dr (Schemes 5a and 5b). Upon treatment with a phosphonium ylide, **3aa** was transformed to conjugated diene nearly quantitatively (**8**), which can undergo Diels-Alder reaction with succinimide leading to product **9** in good yield and 1:2 dr. (Scheme 5c).



Scheme 6. Mechanistic studies.

To gain insight into the current ring expansion coupling system, some preliminary mechanistic studies were conducted. Kinetic isotope effect experiments have been performed under the standard conditions. The KIE was determined to be $k_H/k_D = 2.8$ for the parallel reactions using **1a** and **1a-*d*$_1$** at a low conversion (Scheme 6a). This value indicates that the C-H cleavage process is probably involved in the turnover-limiting process. A metalacyclic complex was synthesized and designated as a catalyst under the standard conditions, giving a moderate yield of **3aa** (Scheme 6b). To gain more information on the ring expansion process, a control experiment was conducted by using an open-chain 1,3-dione as a coupling reagent which had been used for chain expansion by Hesse.[19] As expected, an acyl migration product was obtained albeit in low yield, indicating relevance of a retro-Aldol reaction as in cleavage of the cyclobutane ring (Scheme 6c). A plausible pathway is given in the ESI based on our experimental observations and literature precedents on mechanism studies of Mn(I) catalyzed C-H alkenylation and ring expansion reactions catalyzed by Rh(I) or Re(I).[20]

In summary, by merging C-H activation with carbonyl addition and retro-Aldol addition, we have realized convenient synthesis of seven- and eight-membered carbocycles bearing an exocyclic double bond. The reaction proceeded smoothly under redox-neutral and operationally simple conditions via C-H activation and C-C cleavage with decent chemoselectivities and atom economy. Given the facile construction of seven- or even eight-membered ring skeletons and the structural diversity, the Mn(I)-catalyzed cascade system may find applications in the synthesis of useful carbocycles.

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Conflicts of interest

There are no conflicts to declare.

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