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UPDATE

Manganese-Catalyzed C-H Annulation of Ketimines with Allenes: Stereoselective Synthesis of 1-Aminoindanes

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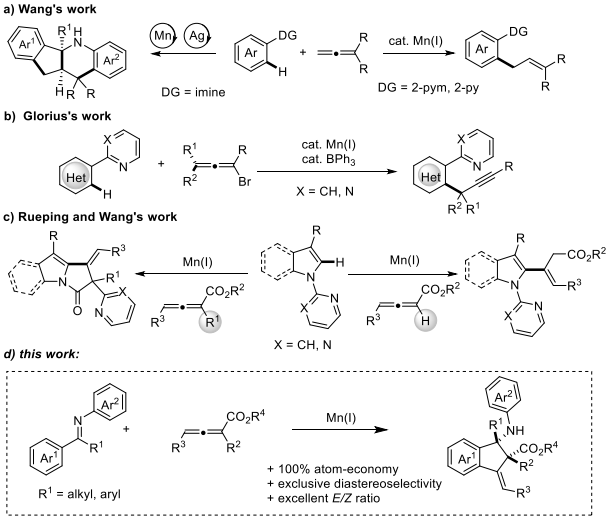
Abstract. A manganese-catalyzed C-H annulation of ketimines with poly-substituted ester-activated allenes toward the synthesis of 1-aminoindanes bearing two vicinal all-substituted carbon stereocenters and an exocyclic double bond was developed. The reaction features high diastereoselectivity, high *E*/*Z* selectivity, 100% atom-economy, broad substrate scope and good functional group tolerance.

Keywords: allene; C-H activation; indane; ketimine; manganese

The recent years have witnessed great advances in metal-catalyzed C-H activation reactions, which enable an efficient assembly of complex molecules from simple starting materials in an atom- and step-economic fashion.[1] So far, however, these catalytic reactions have been arguably over-reliant on precious metals such as palladium, rhodium, iridium, platinum, and ruthenium.[1] For the sake of sustainability, recently, significant efforts have been paid on the employment of earth abundant metals in lieu of those precious metals.[2] In this regard, the manganese-based catalysts show great promise due to their low toxicity, low cost and sometimes, unique working modes.[3] On the other hand, the multi-fold reactivities of allene[4] in metal catalysis have rendered it an intriguing synthon in C-H activation reactions, leading to diverse alkenylation,[5] allylation,[6] allenylation[7] or cyclization[8] products. For instance, under the catalysis of manganese, Wang reported an atom-economic aromatic C-H allylation reaction by using 1,1-disubstitued allenes as coupling partner (Scheme 1a).[9] When *N*-aryl ketimines were used as substrates, an interesting Mn(I)/Ag(I)-cascade catalysis allowed an C-H allylation/Povarov reaction in one-pot to form the complex polycyclic products (Scheme 1a).[10] Glorius recently disclosed an elegant Mn(I)/BPh_3-cocatalyzed direct C-H propargylation using bromoallenes (Scheme 1b).[11] The electron-withdrawing group-activated allenes showed unique reactivity and different regioselectivity. As such, Rueping[12] and Wang[13] independently found that the use of 1,3-disubstituted allenyl esters in Mn(I)-catalyzed C-H activation reaction led to the hydroarylation prodoucts, whereas the employment of poly-substituted allenyl esters in the same reaction gave cyclized products via a C−H alkenylation/Smiles rearrangement cascade, featuring a migration of the heterocyclic directing group (Scheme 1c). The latter reaction, together the reported Mn(I)-catalyzed C-H addition reactions to C-heteroatom unsaturated bonds (including aldehydes,[14] ketones,[14a] imines,[15] isocyanates,[16] and nitriles[14b]) and oxiranes,[17] highlight the strong nucleophilicity of C-Mn bond. Herein, we report our realization of a Mn(I)-catalyzed [3+2] cyclization of aromatic ketimines with allenyl esters by taking advantage of the high nuelcophilicity of C-Mn bond and the unique regioselectivity of the allenes (Scheme 1d). The reaction provides a simple access to 1-aminoindanes[18] bearing two vicinal all-substituted carbon stereocenters and an exocyclic double bond with high diastereoselectivity and *E/Z* selectivity. It should be noted the cycloaddition of aromatic ketimines with allene was known with Re(I)[19] or Rh(I)[20] catalyst. The scope of these reactions was limited to mono-alkyl-substituted allenes.



Scheme 1. Manganese-catalyzed C-H activation with allenes.

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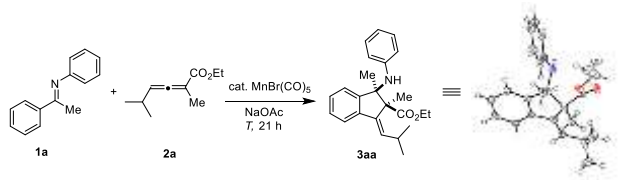
At the outset of our studies, we tested the reaction of aromatic ketamine **1a** with 1,1,3-trisubstituted allenyl ester **2a** (1.5 equiv.) with $MnBr(CO)_5$ (10 mol %) as catalyst in 1,4-dioxane at 100 °C (Table 1). Interestingly, an annulated 2,3-dihydro-1*H*-indene product **3aa** was furnished in 23% yield as a single stereoisomer in the presence of NaOAc (40 mol %) as additive (entry 1). The *cis* configuration and *E* geometry of the product was unambiguously identified by X-ray crystallography analysis.[21] No reaction took place without NaOAc, indicating the important role of base for C-H activation (entry 2). While KOAc showed comparable reactivity (entry 3), HOAc was ineffective for the reaction (entry 4). The screening of solvents demonstrated that the originally used 1,4-dioxane was optimal (entries 5-7). Increasing the loading of **2a** to 2.0 equivalents led to a better yield of 39% (entry 8). The yield could be further improved to 68% by elevation of the temperature to 120 °C (entry 9). A good yield of 82% was obtained by doubling the loading of manganese catalyst (entry 10).

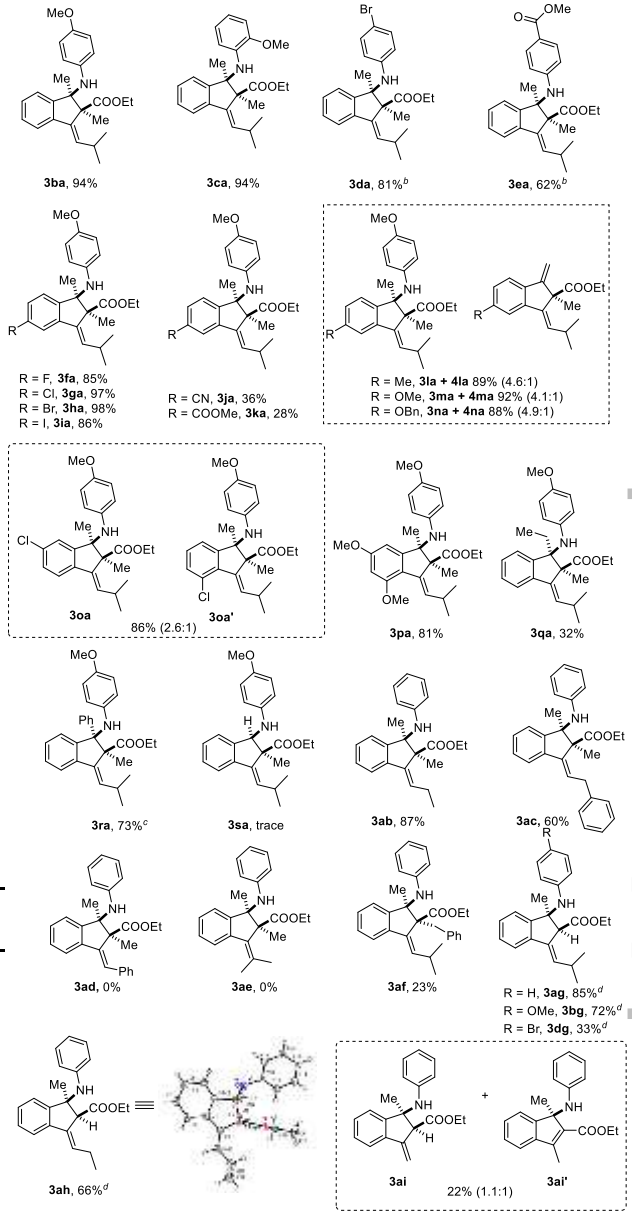
Table 1. Optimization of Mn(I)-catalyzed C-H annulation reaction[a]



entry	**2a** (eq)	Mn (mol %)	additive	Solvent	T [°C]	Yield [%]
1	1.5	10	NaOAc	1,4-dioxane	100	23%
2	1.5	10	-	1,4-dioxane	100	0
3	1.5	10	KOAc	1,4-dioxane	100	22%
4	1.5	10	HOAc	1,4-dioxane	100	0
5	1.5	10	NaOAc	DCE	100	3%
6	1.5	10	NaOAc	toluene	100	0
7	1.5	10	NaOAc	CH_3CN	100	12%
8	2.0	10	NaOAc	1,4-dioxane	100	39%
9	2.0	10	NaOAc	1,4-dioxane	120	68%
10	**2.0**	**20**	**NaOAc**	**1,4-dioxane**	**120**	**82%**

[a]**1a** (0.2 mmol), **2a**, cat. $MnBr(CO)_5$, additive (0.4 equiv.), solvent (1.0 mL), T, 21 h, isolated yield.

Table 2. Mn(I)-catalyzed C-H annulation ketimines with allens[a]

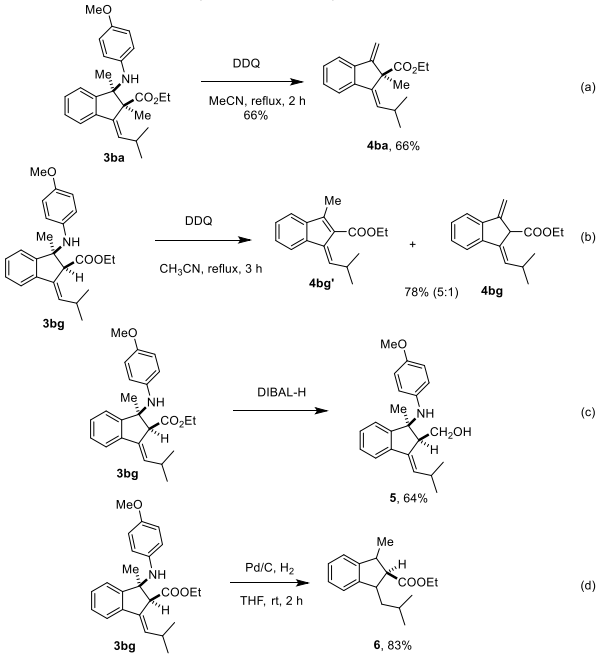


[a]general conditions: **1** (0.2 mmol), **2** (0.4 mmol), $MnBr(CO)_5$ (0.2 equiv.), NaOAc (0.4 equiv.), 1,4-dioxane (1.0 mL), 120 °C, 21 h, isolated yield. [b]NaOAc (1 equiv.) was used, 130 °C. [c]48 h. [d]$MnBr(CO)_5$ (0.1 equiv.), 100 °C.

With the optimized catalytic system in hand, we firstly explored the generality of the reaction by reacting **2a** with a broad range of ketimines **1** (Table 2). Ketimines bearing either electron- donating (**3ba** and **3ca**) or withdrawing groups (**3da** and **3ea**) on the *N*-aryl ring were applicable for cyclization, giving the corresponding products in good to excellent yields. The *para*-halogen functional groups (**3fa**-**3ia**) substituted on the benzene ring of C-H activation were all well tolerated. Stronger electron-withdrawing groups such as cyano (**3ja**) and ester (**3ka**), however, gave significantly lower yields. Interestingly, the electron-donating groups did deliver the cyclization products (**3la**-**3na**) as expected. A minor amount of amino-eliminated products (**4la**-**4na**) were also observed, which could be rationalized by the stabilization of benzylic cation by *para* electron-donating groups (see Scheme 3b). The *meta*-Cl substitution led to two regioisomers (**3oa**:**3oa'** = 2.6:1), with cyclization occurring preferationally at the sterically less crowded position. The 3,5-dimethoxy-substituted substrate gave the desired product (**3pa**) without difficulty, although both of the ortho C-H bonds were sterically shielded. In addition to alkyl aryl ketimines (**3aa**-**3qa**), the diaryl ketimine was also a suitable substrate for the reaction (**3ra**). However, the aldimine only gave trace amount of the corresponding product (**3sa**). The scope on the allene part was also examined. Besides the iso-propyl group,

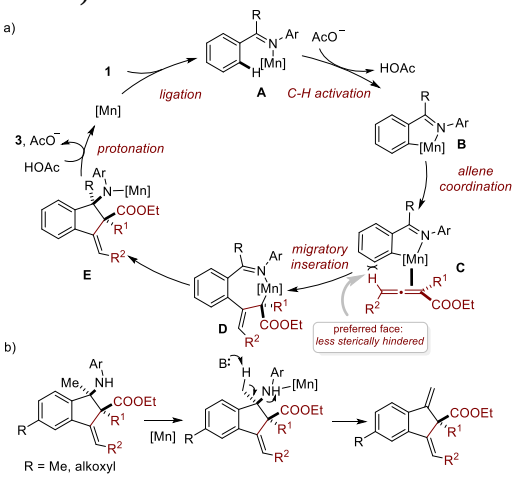
other aliphatic substituents at C3 position of allene, such as ethyl (**3ab**) and benzyl (**3ac**), were also well tolerated, but a phenyl substituent (**3ad**) resulted in no reaction. With an additional methyl group at the C3 position, however, the reactivity was completely shut down probably for steric reasons (**3ae**). A decreased reactivity was also observed with a more sterically demanding C1-benzyl substituent (**3af**). The 1,3-disubstituted allenyl esters were good substrates as well, delivering the *cis*-products in good yields with 10 mol % catalyst loading at 100 °C (**3ag**, **3bg**, **3dg**, **3ah**).[21] The use of terminal allene did give the desired product, but in low yield (**3ai**). The exocyclic double bond-migrated product **3ai'** was also found.

To showcase the synthetic utility of the obtained products, we explored their further diversifications (Scheme 2). The attempt to deprotect the 4-methoxyphenyl group on nitrogen with DDQ resulted in an elimination reaction, giving the corresponding dienes in good yields (Scheme 2a and 2b). The reduction of the ester group in **3bg** with DIBAL-H gave a free alcohol **5** in 64% yield (Scheme 2c). Finally, the hydrogenation of **3bg** with the Pd/H_2 protocol delivered the reduced product **6** bearing three consecutive chiral centers as a single distereroisomer (Scheme 2d).



Scheme 2. Derivatization of the products.

The following mechanistic scenario was proposed to rationalize the observed reaction outcome (Scheme 3a). Initially, the ligation of manganese to the nitrogen atom of imine promotes a C-H activation to form a metallacycle **B**. This process is believed to be assisted by acetate anion present in the reaction mixture. Thereafter, the allene coordination and a subsequent migratory insertion lead to the formation of complex **D**. The unique electronic and steric properties of allene dictate the observed regio- and stereoselectivity in this step. Specifically, the C-Mn bond in **B** attacks the more electron-deficient central carbon of allene from the less sterically hindered face, thereby forming the observed *E*-type exocyclic double bond in the final product. The profound nucleophilicity of the formed C-Mn bond would then trigger an intramolecular nucleophilic addition to the imine moiety, wherein the steric repulsion between the ester and R groups causes a *trans* orientation of these two groups in the final cyclized product. Upon protonation with HOAc, the desired cyclization product **3** is formed and the active catalyst is regenerated. For substrates (**3la-3ma**) bearing electron-donating substituent at the *para* position, the ligation of manganese with the amine group in the initially formed products will trigger an elimination reaction to form the second exocyclic double bond (Scheme 3b).[22]



Scheme 3. A proposed Mechanism.

In summary, a manganese-catalyzed C-H activation/annulation reaction with ester-activated allenes was developed. The protocol offers a simple and efficient method toward the synthesis of 2,3-dihydro-1*H*-indenes bearing two vicinal all-substituted carbon stereocenters and an exocyclic double bond with high diastereoselectivity and *E*/*Z* selectivity. Good functional group tolerance and 100% atom-economy was observed. A possible reaction mechanism was proposed to account for the reaction outcomes. Synthetic transformations of the products were conducted, showcasing their utility. We hope this chemistry will find applications in 1-aminoindane derivative synthesis.

Experimental Section

General Procedure for manganese-catalyzed C-H annulation of ketimines with allenes: Ketimine (0.2 mmol), $MnBr(CO)_5$ (11 mg, 20 mol%), NaOAc (6.6 mg, 40 mol %), 1,4-dioxane (1.0 mL) and allene (0.4 mmol) were placed in a 15 mL Schlenk tube under N_2. The mixture was stirred at 120 °C for 21 h. After cooled to ambient temperature, the reaction mixture was diluted with EtOAc (8 mL). Then H_2O (4 mL) was added, and the resulting mixture was extracted with EtOAc (3×10 mL). The

combined organic layer was washed with brine (10 mL), and then dried over Na_2SO_4. After concentration under reduced pressure, purification by column chromatography on silica gel afforded the desired products **3**.

Acknowledgements

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[21] CCDC 1828758 (**3aa**), CCDC 1828759 (**3ah**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

[22] Control experiments showed that both [Mn] and NaOAc were important for the elimination reaction.

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