C–H Activation

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Manganese-Catalyzed Synthesis of *cis*-β-Amino Acid Esters through Organometallic C–H Activation of Ketimines**

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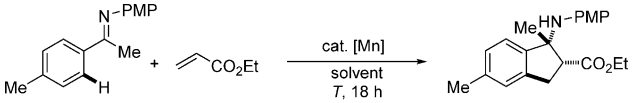
Abstract: *Manganese-catalyzed C–H functionalization reactions of ketimines set the stage for the expedient synthesis of cis-β-amino acid esters through site- and regioselective alkene annulations. The organometallic C–H activation occurred efficiently with high functional group tolerance, delivering densely functionalized β-amino acid derivatives with ample scope.*

As β-amino acids are key structural motifs of non-natural β-peptides and versatile intermediates in organic synthesis,[1] methods for the efficient preparation of substituted derivatives continue to be in high demand. In recent years, catalyzed C–H activation reactions have emerged as an increasingly viable method for improving the step economy of organic syntheses.[2] During the past decade, progress has largely relied on complexes of expensive 4d or 5d noble metals, such as palladium, iridium, or rhodium. In stark contrast, the potential of naturally abundant 3d metal complexes as catalysts for C–H functionalizations is largely untapped.[3] Despite of recent advances with nickel, cobalt, and iron catalysts,[3] manganese complexes are still scarcely employed as catalysts in organometallic C–H activations,[4] although manganese is the third most abundant transition metal after iron and titanium. Thus far, manganese catalysis has been dominated by outer-sphere radical oxygenations or halogenations by high-valent manganese species.[5–7] As a consequence, only sporadic examples of organometallic C–H activation reactions with inexpensive manganese catalysts have been described, with pioneering reports by the groups of Kuninobu and Takai,[8] as well as elegant recent contributions from Wang and co-workers.[9] Within our program on sustainable C–H functionalization processes,[10] we have developed a novel manganese-catalyzed direct synthesis of β-amino acid derivatives from easily available imines by organometallic C–H activation. Notable features of our approach include an excellent functional-group tolerance, an unprecedented manganese-catalyzed C–H activation/alkene annulation process as well as a versatile cascade transformation with unusual *cis* diastereoselectivity.

At the outset of our studies, we tested various reaction conditions for the envisioned C–H functionalization of ketimine **1a** (Table 1). Interestingly, catalytic amounts of $[Mn_2(CO)_{10}]$ directly furnished the *cis*-β-amino acid ester **3aa**

Table 1: Optimization of manganese-catalyzed C–H activation.[a]



1a 2a 3aa

Entry	Catalyst	Solvent	*T* [°C]	Yield [%]
1	$[Mn_2(CO)_{10}]$	toluene	100	59
2	$[Mn_2(CO)_{10}]$	toluene	140	45
3	**$[Mn_2(CO)_{10}]$**	**toluene**	**120**	**87**
4	$[MnBr(CO)_5]$	toluene	120	11[b]
5	$MnCl_2$	DCE	120	–[b]
6	**$[Mn_2(CO)_{10}]$**	**DCE**	**120**	**94**
7	$[Mn_2(CO)_{10}]$	1,4-dioxane	120	77
8	–	DCE	120	–
9	$[Co_2(CO)_8]$	DCE	120	< 3
10	$[Ni(cod)_2]$	DCE	120	–[b]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (5.0 mol%), solvent (1.0 mL), 120°C, 18 h, yields of isolated products given. [b] Catalyst (10 mol%). cod = cyclooctadiene, DCE = 1,2-dichloroethane, PMP = *para*-methoxyphenyl.

(entries 1–3), and additional amines or metal acetate additives were not required for an efficient alkene annulation process. The unusual *cis* configuration of product **3aa** was unambiguously established by detailed two-dimensional NMR spectroscopy.[11] Subsequent optimization studies highlighted the unique activity of the $[Mn_2(CO)_{10}]$ catalyst (entries 3–5) with optimal results being obtained in toluene or DCE as the solvent (entries 3, 6, and 7). Intriguingly, representative cobalt or nickel complexes did not deliver the desired product **3aa**, and unreacted starting materials were reisolated (entries 9 and 10). In stark contrast to a transformation of ketones into indenes that is catalyzed by the expensive 5d rhenium complex $[ReBr(CO)_3(THF)_2]$ at 150–180°C,[12] the new manganese-catalyzed process occurs under considerably milder[13] reaction conditions, thereby allowing for the general assembly of the sensitive β-amino acid motif.

With the optimized catalytic system in hand, we explored its scope for the manganese-catalyzed C–H functionalization of imine **1a** (Scheme 1). A variety of alkenes **2a–d** proved to be suitable substrates, affording the desired *cis*-β-amino esters **3** with excellent regio- and diastereoselectivity. Notably, the

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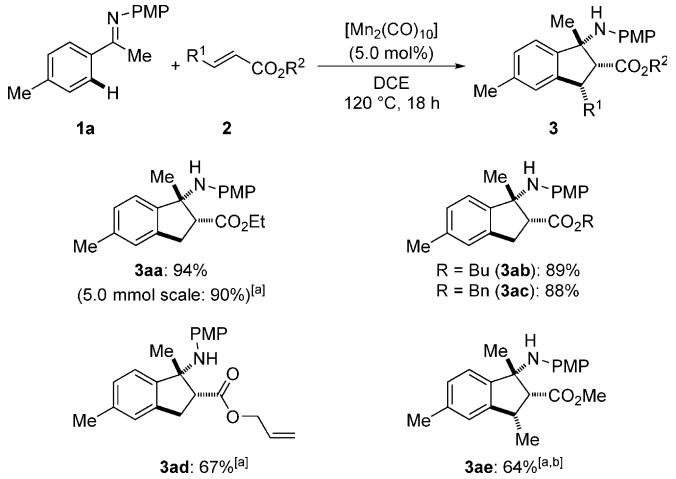
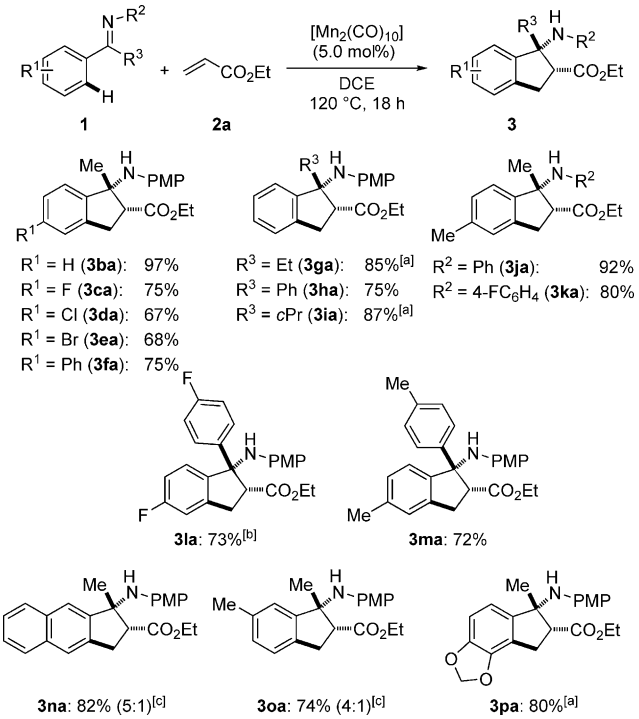


Scheme 1. Manganese-catalyzed C–H functionalization with alkenes **2**. [a] In toluene. [b] With $[Mn_2(CO)_{10}]$ (10 mol%).



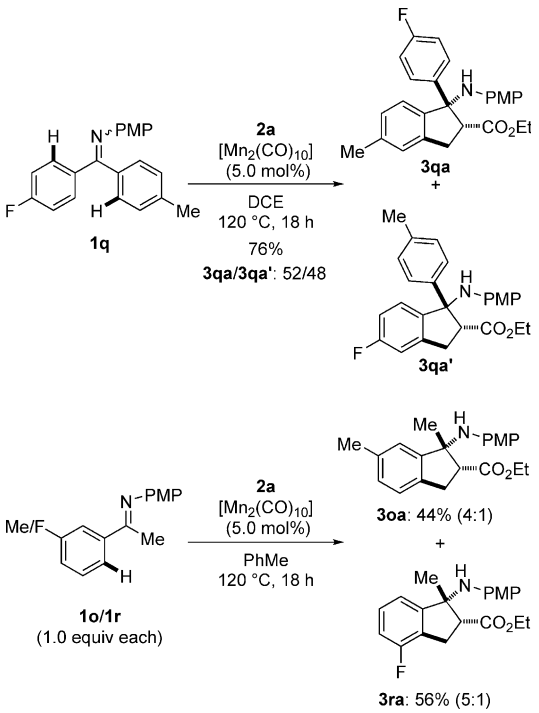
Scheme 2. Manganese-catalyzed C–H functionalization with imines **1**. [a] In toluene. [b] With $[Mn_2(CO)_{10}]$ (10 mol%). [c] Major regioisomer shown; regioisomeric ratios in parentheses.

manganese-catalyzed transformation was not limited to terminal alkenes **2**, but the considerably more challenging internal alkene (*E*)-**2e** was also efficiently converted. Here, the desired product **3ae** was selectively formed with excellent control over all three contiguous stereocenters. In contrast, a (*Z*)-crotonate, a cinnamic acid ester, and a methacrylate gave only traces of the desired products. The robustness of the manganese-catalyzed alkene annulation was reflected by a reaction performed on a 5 mmol scale that gave a comparably high yield.

A broad range of substituted imines **1** were suitable substrates for the manganese-catalyzed transformation (Scheme 2). The catalytic system tolerates a wide range of functional groups, including cyclopropyl, ester, fluoro, chloro, or bromo substituents, which should prove instrumental for further derivatizations of compounds **3**. Generally, both alkyl and aryl ketimines **1** underwent the alkene annulation with comparable levels of efficacy, whereas an aldimine (not shown) furnished only traces of the corresponding product. Particularly, the chemoselective conversion of ethyl-substituted ketimine **1g** at the arene ring is a strong testament to an organometallic C–H activation (see below) as radical transformations would occur at the weaker C_{sp^3}–H bonds. Intramolecular competition experiments of *meta*-substituted arenes **1n** and **1o** were controlled by steric interactions, leading to the predominant formation of regioisomers **3na** and **3oa**, respectively. In contrast, the *meta*-dioxolane substitution pattern of arene **1p** led to site-selective C–H functionalization at the C2 position,[14] which can be rationalized in terms of a secondary directing group effect.

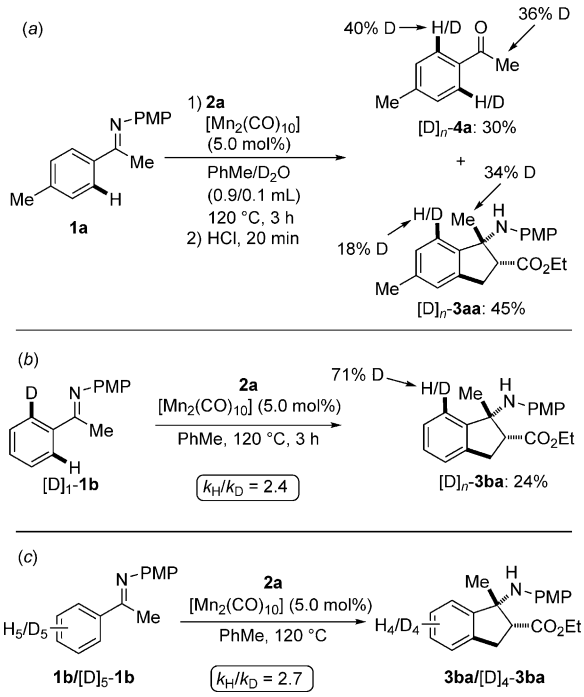
Considering the unique chemo- and stereoselectivity of the new manganese-catalyzed C–H activation, we became intrigued by delineating its mode of action. To this end, we performed intra- and intermolecular competition experiments with arenes **1** bearing different substituents, which showed that the electronic nature of the substituent exerts only a minor influence on the reactivity (Scheme 3).

C–H functionalization reactions conducted in the presence of D_2O as the co-solvent were suggestive of a reversible



Scheme 3. Intra- and intermolecular competition experiments. For **3oa** and **3ra**, the major regioisomer is shown, and the regioisomeric ratios are given in parentheses.

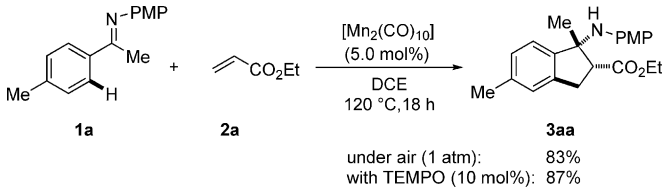
H/D exchange reaction, as was corroborated by the isolation of the partially labeled acetophenone $[D]_n$-**4a** after acidic work-up, along with the labeled product $[D]_n$-**3aa** (Sche-



Scheme 4. H/D exchange experiment and determination of KIEs.

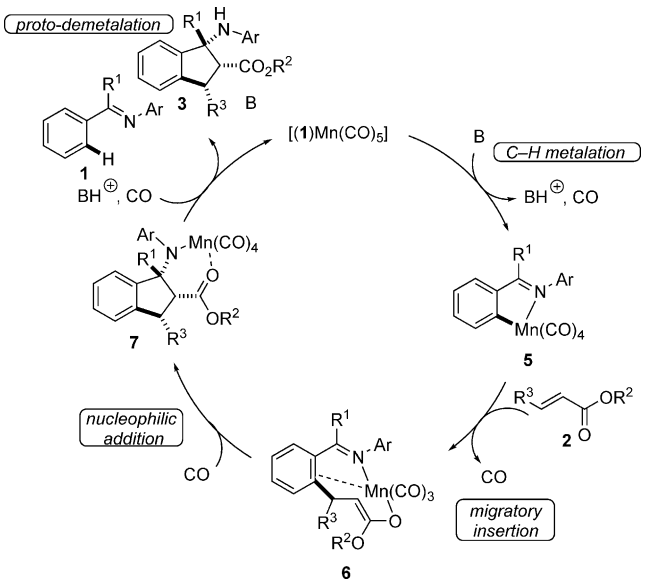
me 4a). The intramolecular kinetic isotope effect (KIE) of the manganese-catalyzed C–H functionalization was found to be $k_H/k_D \approx 2.4$ (Scheme 4b). Moreover, the intermolecular KIE of $k_H/k_D \approx 2.7$ was investigated by means of the initial rates for independent reactions of substrates **1b** and $[D]_5$-**1b** (Scheme 4c). These experimental results are indicative of a kinetically relevant C–H metalation step.

It is noteworthy that the working mode of the organometallic catalyst (see below) was clearly shown by successful manganese-catalyzed C–H functionalizations under an atmosphere of air or in the presence of the radical scavenger TEMPO (Scheme 5). The successful C–H activation of ketimine **1a** in ambient air furthermore highlights the robust nature of the operationally simple manganese-catalyzed transformation.



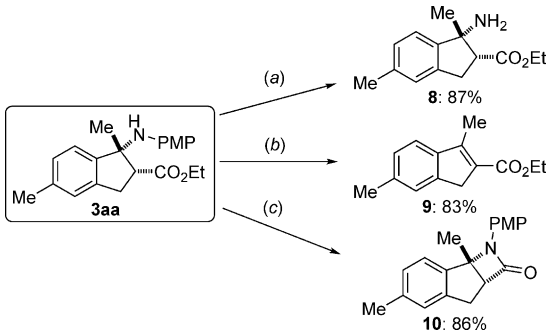
Scheme 5. C–H functionalization in the presence of radical scavengers.

Based on these mechanistic studies, we propose a plausible catalytic cycle for the formation of β-amino esters **3** (Scheme 6). The initial C–H metalation of ketimine **1** is proposed to proceed by base assistance[15] and leads to intermediate **5**. Subsequently, the metallacycle **5** carbomanganates the α,β-unsaturated ester **2** by regioselective migratory insertion of the latter into the Mn–C bond. Through the assistance of the weakly coordinating[16,17] alkyloxycarbonyl group manganese enolate **6** is generated, which thereafter undergoes an intramolecular nucleophilic attack at the carbon atom of the imine moiety, thereby affording complex **7**. The chelation of the imino group and the ester enolate motif by the manganese ion is suggested to facilitate this key cyclization, which in turn leads to the exclusive *cis* diastereoselectivity. Finally, proto-demetalation of amide **7** affords the desired *cis*-β-amino ester **3** and regenerates the catalytically active manganese complex.



Scheme 6. Proposed mechanism.

To illustrate the synthetic utility of the obtained β-amino esters **3** we explored their further diversification (Scheme 7). Thus, compound **3aa** was selectively converted into β-amino ester **8**, which displays the free amino group (Scheme 7a). The power of the manganese-catalyzed C–H activation approach was finally demonstrated by the step-economical synthesis of the useful building block **9** (Scheme 7b) as well as the versatile β-lactam scaffold of compound **10** (Scheme 7c).



Scheme 7. Diversification of product **3aa**. Reagents and conditions: a) CAN (2.5 equiv), CH_3CN/H_2O (1:1), 23 °C, 3 h. b) Toluene, 160 °C, 14 h. c) LiHMDS (1.5 equiv), THF, 0 °C→23 °C, 10 h. CAN = ceric ammonium nitrate, LiHMDS = lithium bis(trimethylsilyl)amide.

In summary, we have reported the first manganese-catalyzed[18] alkene annulation by C–H activation, providing expedient access to valuable β-amino acid esters in a step-economic fashion. The operationally simple transformation features high catalytic efficacy, good functional-group tolerance, and an unusual *cis* stereoselectivity. The power of the manganese-catalyzed organometallic C–H activation process was reflected by the excellent regio- and chemoselectivity, in particular, which enabled the synthesis of sensitive β-amino acid esters under comparably mild reaction conditions.

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Communications

C–H Activation

W. Liu, D. Zell, M. John,
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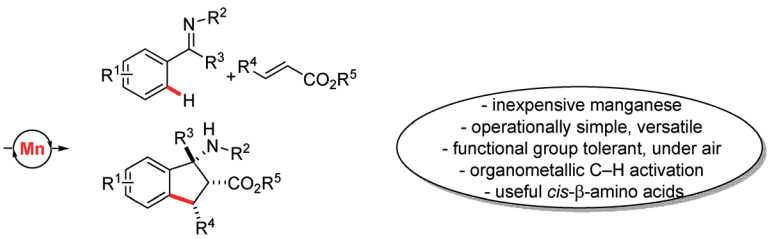
Manganese-Catalyzed Synthesis of *cis*-β-Amino Acid Esters through Organometallic C–H Activation of Ketimines



An operationally simple manganese-catalyzed C–H functionalization of ketimines provides access to β-amino acid esters. The mechanism of this transformation was studied, and its utility proven by further modifications of the synthetically useful β-amino acid esters into attractive compounds.

