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Divergence in CH alkylation of indoles under Mn catalysis†

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Achieving divergence in CH alkylation of substrates using feedstock chemicals is an attractive paradigm to enable the production of diverse products from the same starting materials. Herein, we report manganese-catalyzed CH alkylation of indole/indolines with alcohols, where product selectivity is achieved through catalyst control. By use of a molecularly defined PNP–Mn(I) complex, tandem double dehydrogenative CH alkylation of indoles is observed. In contrast, an NNN–Mn(II)-based catalyst system provides a diverse range of value-added bis(indolyl)methanes (BIMs) *via* an interrupted borrowing hydrogen strategy. The present strategy was successfully applied for sustainable, scalable synthesis of several life science molecules (vibrindole A, turbomycin B alkaloid, and antileukemic and anticancer agents) and natural products (gramine, dipterine, *etc.*).

Introduction

Indole scaffolds are ubiquitous in the core structure of many natural and unnatural bioactive compounds, active pharmaceuticals, and agrochemicals and have prominent industrial applications.[1] Various drugs like gramine, serotonin, tryptophan, corynantheine, oxypertine, bufotenine, and melatonin contain indole motifs.[2] It is worth noting that ten of the top 200 best-selling small-molecule drugs of 2022 are indole derived with a global market share of nearly US $17.45 billion.[3] Notably, several life science molecules contain C-alkylated indole units (Fig. 1). Thus, the widespread application of the indole moiety has attracted considerable attention to develop novel and sustainable catalytic methods for indole framework synthesis and selective modification.[4] The method often applied to access C3-alkylated indoles is the Lewis acid-catalyzed Friedel–Crafts reaction using alkyl halides.[5] However, the use of expensive and mutagenic haloalkanes makes the classical strategies unaffordable. Indeed, these strategies have inherent limitations, such as the generation of excessive toxic waste and poor regioselectivity.

Recently, transition-metal-catalyzed acceptorless dehydrogenation and borrowing hydrogen (BH) strategies have emerged as powerful tools in chemical synthesis.[6,7] These strategies are widely employed for C–C and C–N alkylation reactions.[7] Indeed, this method uses alcohols as alkylating reagents as a benign and economical alternative to alkyl halides. Notably, the total number of available commercial alcohols is much higher than the number of alkyl halides.[8] Likewise, C3 alkylation of indoles has been explored under borrowing hydrogen catalysis using precious transition metal catalysts such as Pd, Ir, and Ru.[9] Recently, earth-abundant first-row transition metal complexes of Co, Mn, Fe, Cu, *etc.*, with an elegant ligand backbone, have been used as an alternative to these expensive catalysts.[10,11] Wang and co-workers[12] reported an iridium-catalyzed hydrogen auto-transfer method for the C3 alkylation of indoles by directly employing indoline and alcohols as coupling partners. The research group of Kundu reported an Ir-

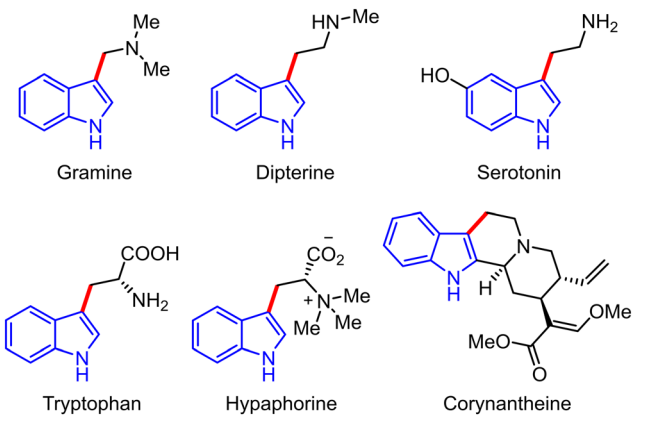

Fig. 1 Natural products and pharmaceutical compounds containing 3-substituted indole motifs (selected examples).

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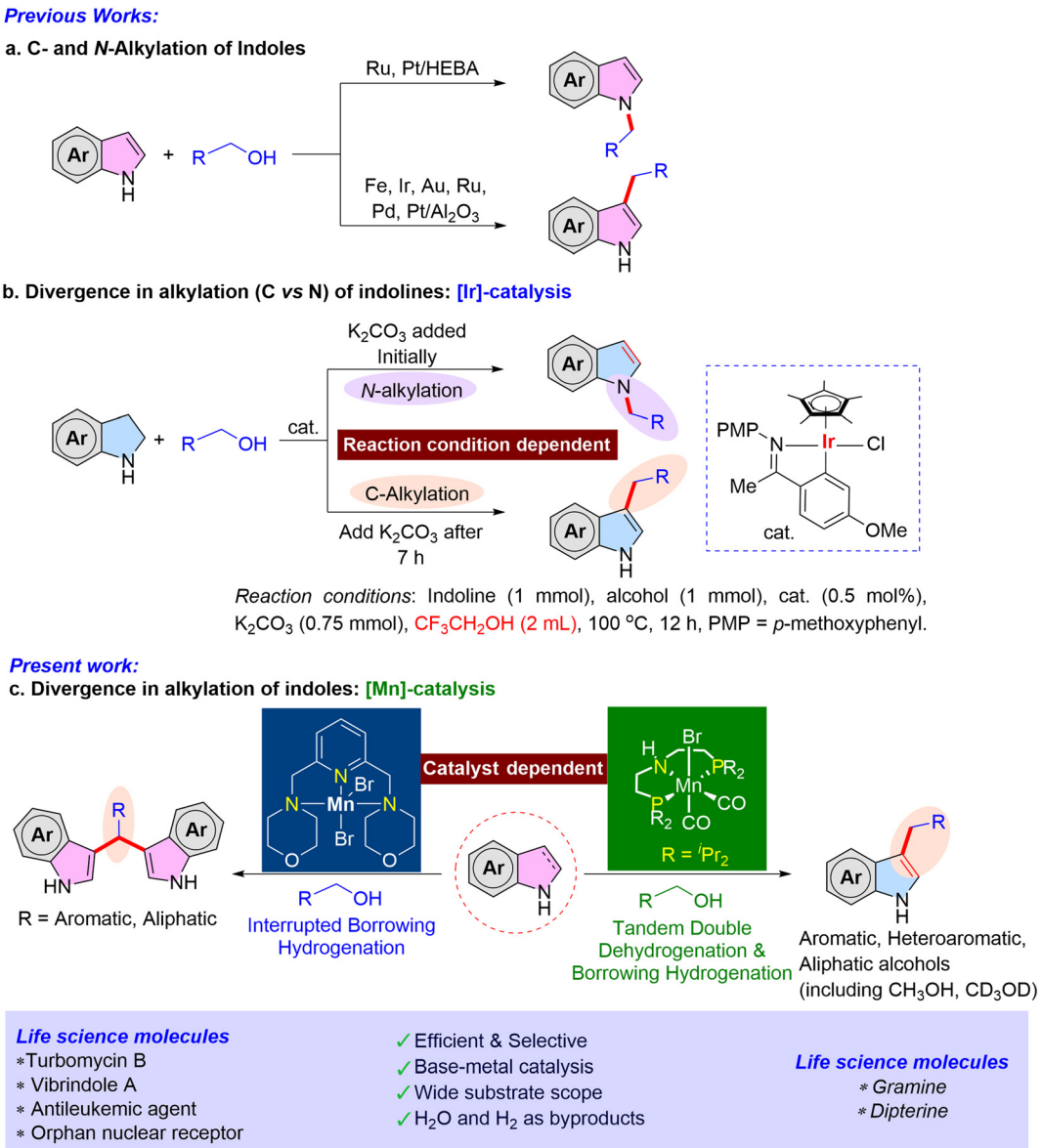
† Electronic supplementary information (ESI) available: General information, experimental details, control experiments, kinetic studies, synthesis and characterization of products, copies of ^{1}H and ^{13}C NMR, and X-ray data of [**Mn-5**]. See DOI: **https://doi.org/10.1039/d3cy01044a**

catalyzed oxidative dehydrogenative coupling of indolines and alcohols to C3-alkylated indoles.[13] A seminal work on manganese-catalyzed regioselective dehydrogenative *C- versus N*-alkylation enabled by a solvent switch was reported by Rueping and co-workers under Mn catalysis.[14] Of late, Srimani and co-workers reported a manganese-catalyzed selective C3 functionalization of indoles and bis(indolyl) methane (BIM) derivative synthesis by tuning the reaction parameters.[15]

Equally, BIMs are essential molecules and play a vital role in organic synthesis and natural product chemistry. Several BIM derivatives exhibit pharmacological activities, including antimicrobial, antifungal, antibacterial, and anticancer.[16] With this background, herein we develop an expedient, Mn-catalyzed strategy for the direct coupling of indolines with alcohols (aromatic, heterocyclic, and aliphatic alcohols) to access C3-alkylated indoles with the liberation of hydrogen gas. The present strategy involves double acceptorless dehydrogenation (indoline to indole and alcohols to aldehydes) and subsequent borrowing hydrogenation. This reaction is catalyzed by a single-site PNP–Mn(I) complex. Interestingly, under similar catalytic conditions, the NNN–Mn(II) system offered a diverse range of bis(indolyl) methanes.[11e] In the latter case, direct dehydrogenative coupling of indoles with alcohols followed by the IBH reaction is operative. Several drug molecules, such as gramine, dipterine, vibrindole A, and turbomycin B alkaloids, have been synthesized using our strategy under benign conditions. Such catalytic cascade dehydrogenative transformation of alcohols that enables divergence in CH



Scheme 1 Transition-metal catalyzed chemodivergence in *C*- and *N*-alkylation of indoles/indolines.

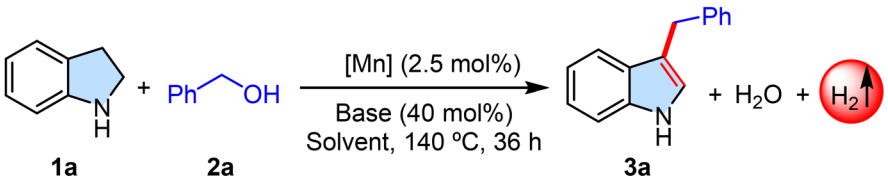
alkylation of indoles under base metal catalysis is unprecedented (Scheme 1).

Results and discussion

The development of sustainable, earth-abundant, and non-precious transition-metal-based catalytic systems (Cu, Ni, Co, Fe, and Mn) is becoming more appealing for the replacement of noble rare-element-based catalytic chemical production.[10,17] Such an attractive replacement contributes to preserving rare precious metal resources and brings new reactivity and selectivity patterns. In recent years, there has been growing evidence that molecular manganese complexes can be potential catalysts for (de)hydrogenation and related reactions.[17,18]

Based on previous literature reports, we synthesized four different molecularly defined Mn(I)–PNP pincer complexes, *i.e.*, **Mn-1** to **Mn-4**, for our initial studies (Table 1).[17a] With the above complexes, we started screening C3 alkylation by considering indoline **1a** and benzyl alcohol **2a** as model substrates. To our delight, performing the reaction between **1a** and **2a** with a catalytic amount of **Mn-1** complex and base resulted in a 67% isolated yield of the desired product **3a** within 24 h. By increasing the time to 36 h, 84% yield of the product was obtained (Table 1, entries 1 and 2). Notably, the reaction requires a low catalyst loading, 2.5 mol% [Mn], and works efficiently with 40 mol% KO^{t}Bu. Lowering the reaction temperature from 140 °C (silicon oil bath temperature) decreases the yield of **3a** to 53% (Table 1, entry 3). Screening other bases and their quantity, we observed that KO^{t}Bu is the most efficient base for the present Mn(I)–PNP-catalyzed tandem double acceptorless dehydrogenation/borrowing hydrogenation (Table 1, entries 4–7). A study on the solvent effect reveals that anhydrous toluene is the optimal solvent for this alkylation reaction (Table 1, entries 2 and 8–10; for more details on the effect of base and solvent, see the

Table 1 Optimization of the reaction conditions[a]



Entry	[Mn]	Base	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	**Mn-1**	KO^{t}Bu	Toluene	140	24	67
2	**Mn-1**	KO^{t}Bu	Toluene	140	36	84
3	**Mn-1**	KO^{t}Bu	Toluene	130	36	53[c]
4	**Mn-1**	LiO^{t}Bu	Toluene	140	24	nd
5	**Mn-1**	NaO^{t}Bu	Toluene	140	24	19[c]
6	**Mn-1**	KHMDS	Toluene	140	24	22[c]
7	**Mn-1**	Cs_2CO_3	Toluene	140	36	71
8	**Mn-1**	KO^{t}Bu	Diphenyl ether	140	36	70
9	**Mn-1**	KO^{t}Bu	*n*-Octane	140	36	42[c]
10	**Mn-1**	KO^{t}Bu	1,4-Dioxane	140	36	29[c]
11	**Mn-2**	KO^{t}Bu	Toluene	140	36	88(98)[d]
12	**Mn-3**	KO^{t}Bu	Toluene	140	36	72
13	**Mn-4**	KO^{t}Bu	Toluene	140	36	80(86)[d]
14	**Mn-2**	KO^{t}Bu	Toluene	140	36	65[e]
15	**Mn-5**	KO^{t}Bu	Toluene	140	24	NR

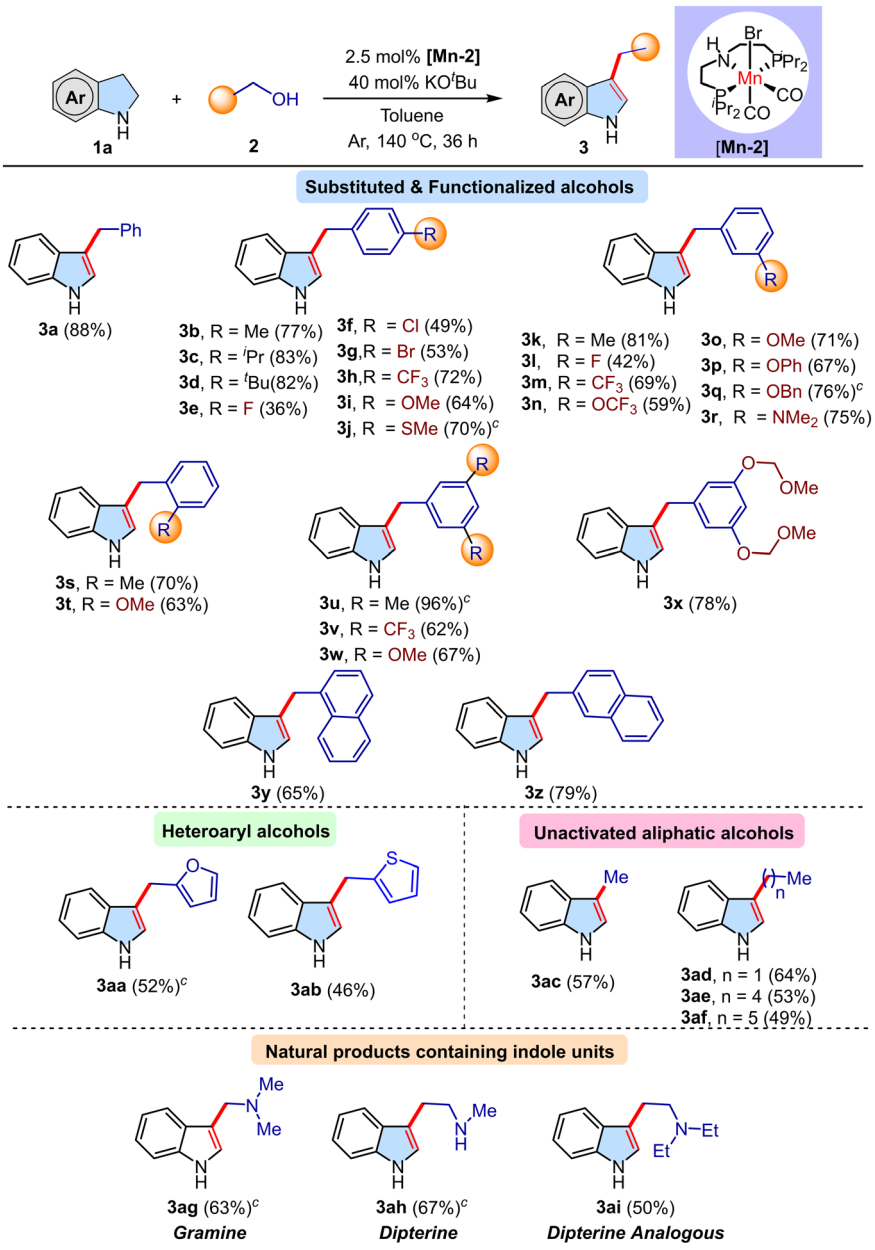
Mn-1, R = Ph
Mn-2, R = ^{i}Pr
Mn-3, R = ^{t}Bu
Mn-4, R = Cy

[a] Reaction conditions: **1a** (0.60 mmol), **2a** (0.90 mmol), cat.[Mn] (2.5 mol%), KO^{t}Bu (40 mol%), dry toluene (2 mL), 36 h in an open Ar atm. [b] Yield of the isolated product. [c] Yields of product **3a** were determined by GC using *m*-xylene as an internal standard, nd = not detected. [d] GC conversion of indoline using *m*-xylene as an internal standard given in parenthesis.

Experimental section in the ESI†). Interestingly, the catalyst [**Mn-2**] gave 88% yield, the highest isolated yield of **3a** among all the manganese complexes screened under identical conditions, and was benchmarked as the optimal catalyst for further studies (Table 1, entries 2 and 11–13). Notably, the *in situ* generated complex also provided the same yield. A reduced base mol% loading resulted in lowering the yield of the desired product **3a** (Table 1, entry 14). Under standard reaction conditions, the newly synthesized NNN–Mn complex **Mn-5** (see the ESI†) did not yield product **3a**.

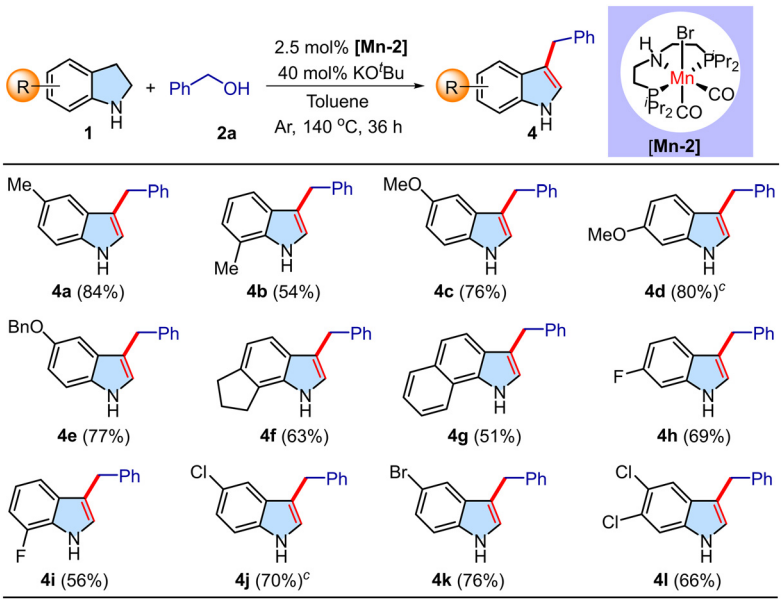
With these optimized reaction conditions in hand, we investigated the scope of indolines and alcohols to illustrate the versatility of the present Mn(I)–PNP-catalyzed CH alkylation of indolines with the liberation of hydrogen gas (Tables 2–4). Considering the model substrate **1a** as a benchmark, a wide variety of alcohols, from benzyl alcohols to primary aliphatic alcohols, were subjected to the optimal conditions to evaluate their reactivity. From the study of the scope of alcohols, benzyl alcohol derivatives were found to be excellent candidates for this transformation. Benzyl alcohol, having a wide array of sensitive functional groups such as –F,

Table 2 Robustness of Mn(I)–PNP-catalyzed CH alkylation of indolines: Scope of alcohols[a,b]



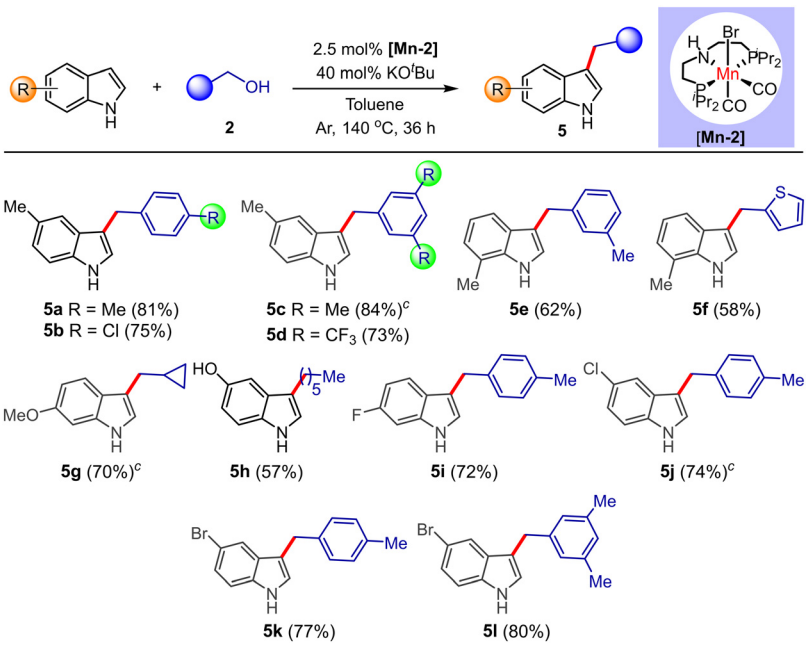
[a] Reaction conditions: **1a** (0.6 mmol), **2** (0.9 mmol), cat.[**Mn-2**] (2.5 mol%), KO^{t}Bu (40 mol%), toluene (2.0 mL), 140 °C (oil-bath temperature), 36 h, Ar atm. [b] Isolated yields. [c] Yield is based on an experiment conducted on a 5.0 mmol scale (5 mol% cat.[**Mn-2**]).

Table 3 Robustness of Mn(I)–PNP-catalyzed CH alkylation of indolines: scope of indolines[a,b]



[a] Reaction conditions: **1** (0.6 mmol), **2a** (0.9 mmol), cat.[**Mn-2**] (2.5 mol%), KO^{t}Bu (40 mol%), toluene (2.0 mL), 140 °C (oil-bath temperature), 36 h, Ar atm. [b] Isolated yields. [c] Yield is based on an experiment conducted on a 5.0 mmol scale (5 mol% cat.[**Mn-2**]).

Table 4 Mn(I) –PNP-catalyzed CH alkylation of indoles: scope of indoles and alcohols[a,b]



[a] Reaction conditions: indoles (0.6 mmol, 1.0 equiv.), alcohols (0.9 mmol, 1.5 equiv.), cat.[**Mn-2**] (2.5 mol%), KO^{t}Bu (40 mol%), anhydrous toluene (2.0 mL), 140 °C (oil-bath temperature), 36 h, Ar atm. [b] Isolated yields. [c] Yield is based on an experiment conducted on a 5.0 mmol scale (5 mol% cat.[**Mn-2**]).

–Cl, –Br, –SMe, –OCF_3, –OPh, and –OBn at different positions of the aromatic ring, was well tolerated and smoothly proceeded to yield the desired products. The unsubstituted benzyl alcohol and its *para*-substituted derivatives with electron-donating groups gave the desired products (**3a**–**3d** and **3i**–**3j**) in very good yields (64–88%). Also, *meta*-substituted benzyl alcohols with –Me, –OMe, –OPh, –OBn, and –NMe_2 groups gave the corresponding desired products (**3k**, **3o**–**3r**; up to 81% yield). The presence of an electron-deficient halogen atom or a –CF_3 group at the

para-position of the benzyl alcohol reduced the reactivity of the alcohol and yielded the desired products (**3f–3h**) in moderate to good yields (49–72%). Similarly, *meta*-substituted benzyl alcohols with $-CF_3$ and $-OCF_3$ groups gave the corresponding desired products (**3m–3n**) in moderate to good yields (59–69%). However, the –F attached C3-alkylated indoles **3e** and **3l** were obtained in poor yields of 36% and 42%, respectively. Methyl and methoxy groups at the *ortho*-position of the benzyl alcohol gave the corresponding products **3s** and **3t** in 70% and 63% isolated yields, respectively. This result indicated that the steric effect does not play a critical role in the initial dehydrogenation step. Moreover, the electronically biased 3,5-disubstituted benzyl alcohols underwent the reaction smoothly and gave the corresponding products **3u–3w** in good to excellent yields (62–96%). The 3,5-bis-acetal substituted product **3x** was obtained in a high isolated yield of 78%.

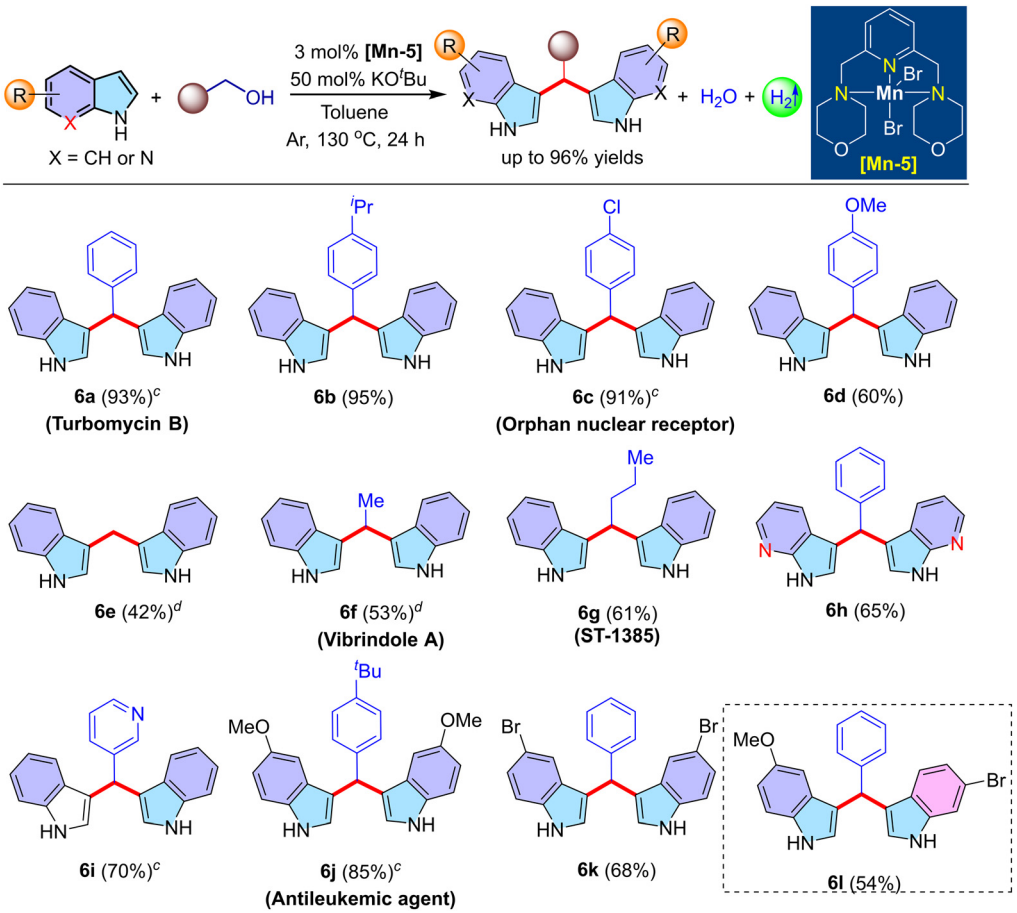
Favorably, 1-naphthylmethanol and 2-naphthylmethanol were subjected to catalytic conditions, and the corresponding C3-substituted indoles **3y** and **3z** were obtained in good yields (65% and 79%, respectively). Additionally, heteroaromatic furfuryl alcohol and 2-thiophene methanol underwent the C3 alkylation reaction and gave the corresponding products **3aa** and **3ab** in 52% and 46% isolated yields, respectively. Interestingly, when aliphatic alcohols were reacted with indoline under optimal conditions, the corresponding C3-alkylated indoles **3ac–3af** were obtained in 49–64% isolated yields. Interestingly, we extended our strategy to obtain natural products gramine (**3ag**) and dipterine (**3ah**) with good yields in a one-step and one-pot manner. Gramine is an important antiviral and antibacterial agent, whereas dipterine is a less popular psychedelic drug. Also, we have synthesized an analogous dipterine-like molecule **3ai** with a 50% isolated yield. Thus, the present PNP–Mn(I)-catalyzed CH alkylation strategy proceeding *via* tandem double acceptorless dehydrogenation/borrowing hydrogenation is general and shows a broad substrate scope with excellent functional group tolerance.

Next, keeping benzyl alcohol (**2a**) as the benchmark substrate, we have shown substrate scope with respect to indoline to demonstrate the generality of this reaction. Several electronically diverse indolines were employed under the present catalytic conditions, and we observed that the reaction proceeds smoothly and yields the desired C3-alkylated products in excellent yields. The methyl-group-substituted indolines gave the corresponding products **4a** and **4b** with 84% and 54% yields, respectively. The reduction of yield in the case of **4b** may be attributed to the steric hindrance influence of the methyl group at the 7-position of the phenyl ring. Electron-donating methoxy-group-substituted indolines participated in the formation of **4c** and **4d** with 76% and 80% yields, respectively. 5-Benzyloxyindoline gives the product **4e** with a 77% isolated yield. The aliphatic ring containing indoline yielded the desired product **4f** with a 63% yield. The π-extended indoline produced the product **4g** with a 51% yield. This is due to the steric influence of the 7th position of indoline. Strong electron-withdrawing fluoro-substituted indolines afforded the desired products **4h** and **4i** with 69% and 56% yields, respectively. The 5-chloro- and 5-bromo substituted indoline yielded the product **4j** and **4k** with 70% and 76% yields, respectively. Indeed, the 5,6-dichloro-substituted indoline provided the desired product **4l** with a 66% isolated yield.

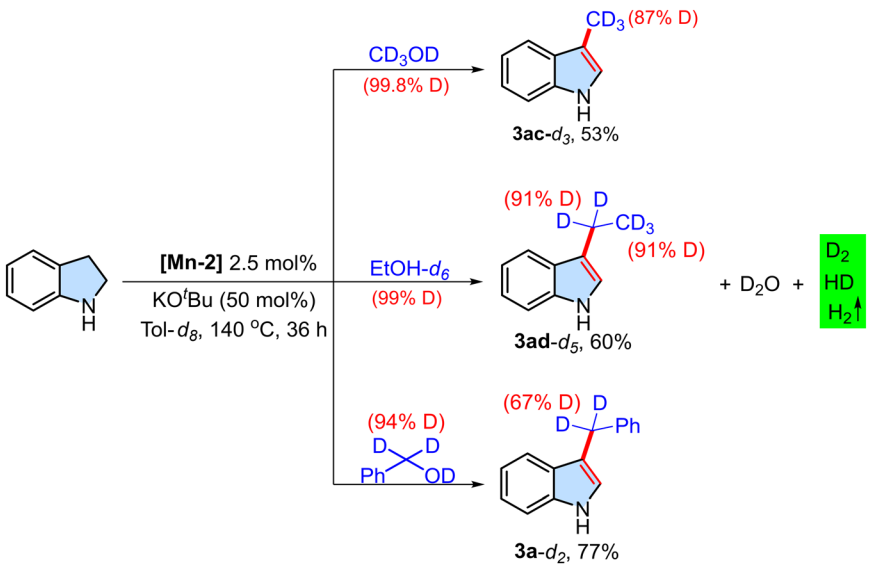
Notably, indole (instead of indoline) smoothly reacted with alcohols and yielded the CH-alkylated product in excellent yields. It was observed that both indoline and indole showed similar reactivity in the present Mn(I)–PNP catalysis. Thus, the initial dehydrogenation of indoline is not the rate-determining step. For the generality of the reaction, we have varied both the alcohol and the indole substrate scope. In most of the cases, we observed an excellent yield of the products. The methyl-substituted indole and benzyl alcohol derivatives yielded the products (**5a–5d**) in up to 84% yields. 7-Methylindole and 3-methylbenzyl alcohol, and 2-thiophenemethanol, gave the desired products **5e** and **5f** with 62% and 58% yields, respectively. Under our optimal conditions, cyclopropylmethanol and 6-methoxyindole gave the corresponding C3-alkylated indole **5g** in 70% isolated yield. Interestingly, the reaction of 5-hydroxyindole with hexanol produced the expected product **5h** with a 57% isolated yield. 6-Fluoroindole and 4-methylbenzyl alcohol gave the product **5i** in 72% isolated yield. Other halo-substituted indoles with substituted benzyl alcohols produced the desired products (**5j–5l**) up to 80% yield.

A complete change in reactivity pattern was observed when the Mn(II)–NNN complex was employed for the dehydrogenative coupling of indole with alcohol. Thus, under similar reaction conditions, the Mn(II)–NNN complex produced bis(indole)methanes (BIMs) as a major product instead of the CH-alkylated product. This reaction proceeds *via* dehydrogenation followed by a Michael-type addition. Here, BIM is the sole product with the liberation of molecular hydrogen, and no formation of C3-alkylated indole was detected. This result indicates that the final (transfer) hydrogenation of the cyclic imine intermediate is slower than the Michael-type addition in the case of the Mn(II)–NNN catalytic system. Thus, Mn(II)–NNN follows an interrupted borrowing hydrogen (IBH) strategy.[19] Notably, the *in situ* generated [**Mn-5**] complex did not yield the expected product in good yield (~53% BIM). This result demonstrates the necessity and importance of molecularly defined complexes. This protocol has been successfully employed on a variety of indoles and alcohols (aromatic and aliphatic, including MeOH) to form a C–C bond through the IBH method (Table 5). Reasonably good substrate scope, functional group tolerance, and good-to-excellent yields are the highlights of the present protocol. To our delight, several life science molecules such as turbomycin B alkaloid (**6a** in 91% yield), vibrindole A (**6f** in 72% yield), molecules with an orphan nuclear receptor (**6d** in 60% yield) and antileukemic properties (**6j** in 85% yield), and ST-1385 (**6g** in 75% yield) were synthesized in excellent yields under our Mn(II)–NNN

Table 5 Mn(II)–NNN-catalyzed synthesis of bis(indolyl)methanes from indoles and alcohols[a,b]



[a] Reaction conditions: alcohol (0.5 mmol), indole (0.5 mmol), catalyst [**Mn-5**] (3 mol%), KO^{t}Bu (50 mol%), and toluene (2.0 mL) were heated at 130 °C (oil-bath temperature) for 24 h under Ar atm. [b] Isolated yields. [c] Yield is based on an experiment conducted on a 5.0 mmol scale (5 mol% cat.[**Mn-5**]). [d] The reaction was performed with alcohol (1 mL) under neat conditions, cat.[**Mn-5**] (10 mol%), and KO^{t}Bu (1.0 eq.) for 36 h under Ar atm.

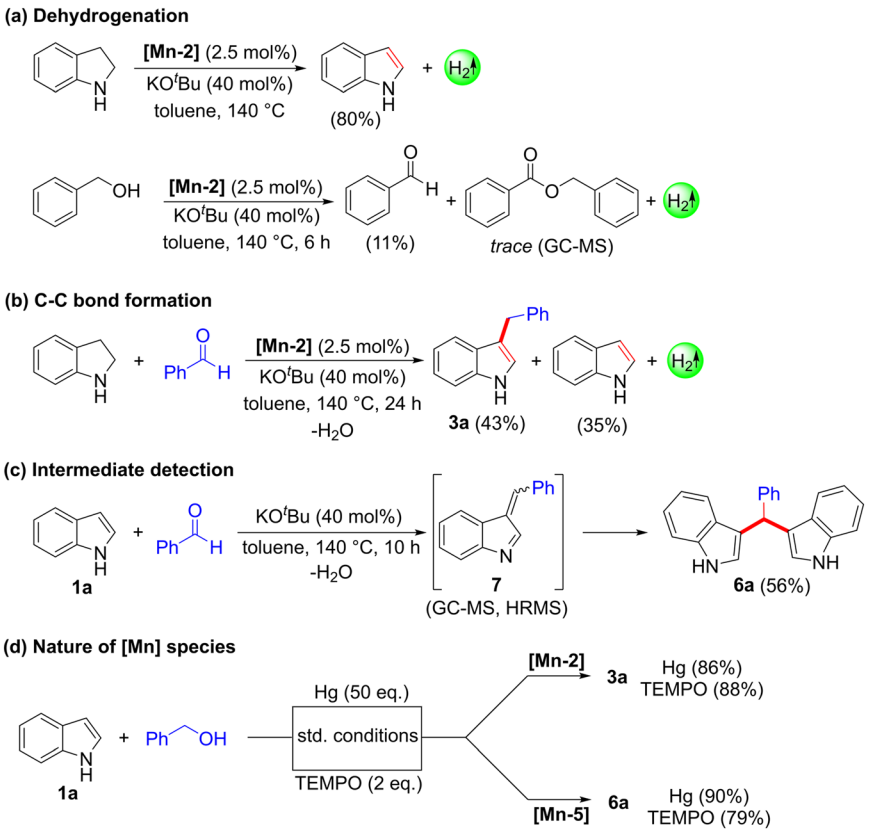


Scheme 2 Mn(I)–PNP-catalyzed CH alkylation of indoline with deuterated alcohols.

catalysis. Interestingly, under the present [**Mn-5**]-catalyzed conditions, an equimolar mixture of 6-bromoindole and 5-methoxyindole smoothly reacted with benzyl alcohol and yielded the unsymmetrical bis(indolyl)methane **6l** in 54% isolated yield along with the formation of symmetrical products. Thus, it is concluded that the present tandem C–C bond formation proceeding *via* tandem dehydrogenation/interrupted borrowing hydrogen is general, selective, and compatible with a wide variety of substrates.

After establishing the reaction conditions, substrate scope, gram-scale synthesis (products **3i**, **3q**, **3u**, **3ag**, and **3ah** in Table 2; products **4d** and **4j** in Table 3; products **5c**, **5g** and **5j** in Table 4; products **6a**, **6c**, **6i** and **6j** in Table 5) applications in life science molecule synthesis, and generality of the present C–C bond forming reactions *via* tandem double dehydrogenation/BH and dehydrogenation/BH strategies, we were interested in mechanistic studies (Schemes 2 and 3 and Fig. 2). Thus, several control experiments were performed under standard reaction conditions. A deuterium labeling experiment of indoline and methanol-d_4 afforded the desired product **3ac**-d_3 with 53% yield and 87% deuterium incorporation (Scheme 2a). Likewise, the reaction of indoline and ethanol-d_6 produced the product **3ad**-d_5 with 60% yield and 91% deuterium incorporation. Deuterated benzyl alcohol **2a**-d_3 reacted with indoline and generated the product **3a**-d_2 with 77% yield and 67% deuterium incorporation (Scheme 2c). Less D incorporation in the product could be due to the H/D exchange with the *in situ* formed H_2O. These results confirm that the reaction proceeds *via* the borrowing hydrogen path. Qualitative gas analysis using an OmniStar™ gas analyzer shows the formation of D_2, HD, and H_2 (see the ESI†). We failed to quantify the hydrogen gas in the ADC coupling reaction. We believe that the active metal-hydride species may be stable only under hydrogenation conditions.

Control experiments show that a single-site manganese catalyst, *i.e.* Mn(I)–PNP complex [**Mn-2**], dehydrogenates both indoline and benzyl alcohol to indole and benzaldehyde under acceptorless conditions, respectively. We observed 85% conversion of indoline and 80% yield of indole by GC analysis under optimal conditions (Scheme 3a). Under standard reaction conditions (in the absence of **1a**), after a short reaction time of 6 h, benzyl alcohol is converted to benzaldehyde (11%) and a trace amount of benzyl benzoate under catalytic conditions (Scheme 3b). An independent reaction of indoline and benzaldehyde afforded the desired product (**3a**) in a 43% isolated yield under Mn(I)–PNP catalysis. Indeed, the intermediate aldehyde was completely consumed, and other competing base-mediated reactions were also observed (Scheme 3c). This result indicates that *in situ* (slow) formation of the alcohol dehydrogenated product, *i.e.*, aldehyde, is very important to achieve the maximum yield of the CH-alkylated product. A simple base-mediated condensation between indole and benzaldehyde gives an imine intermediate (7). Compound 7 was detected by GC as



Scheme 3 Mechanistic studies.

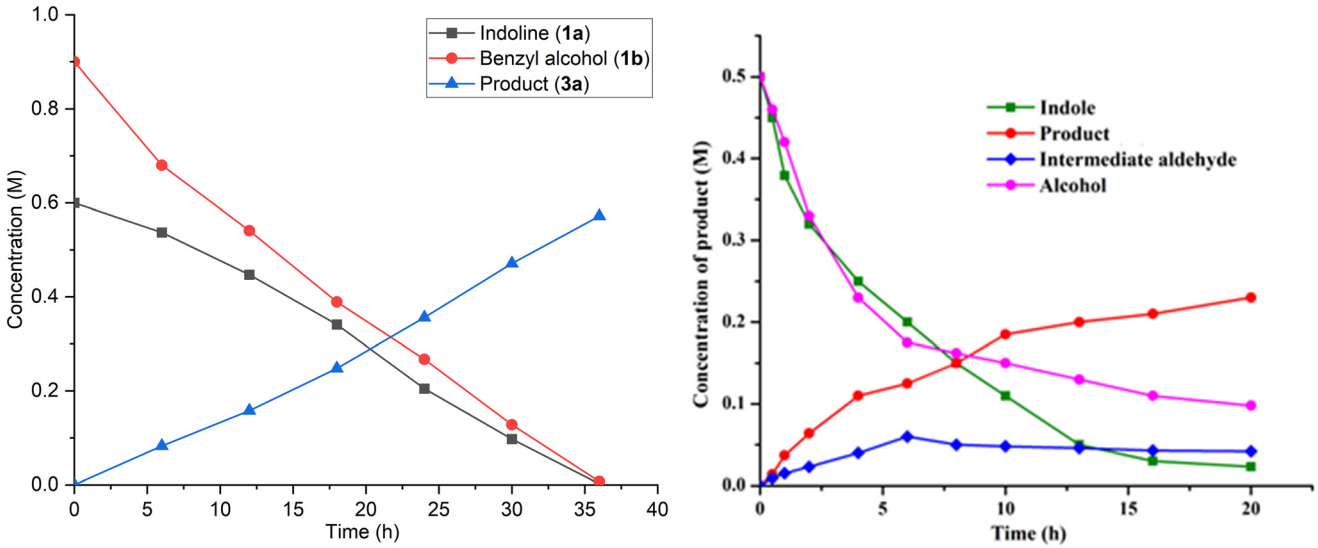
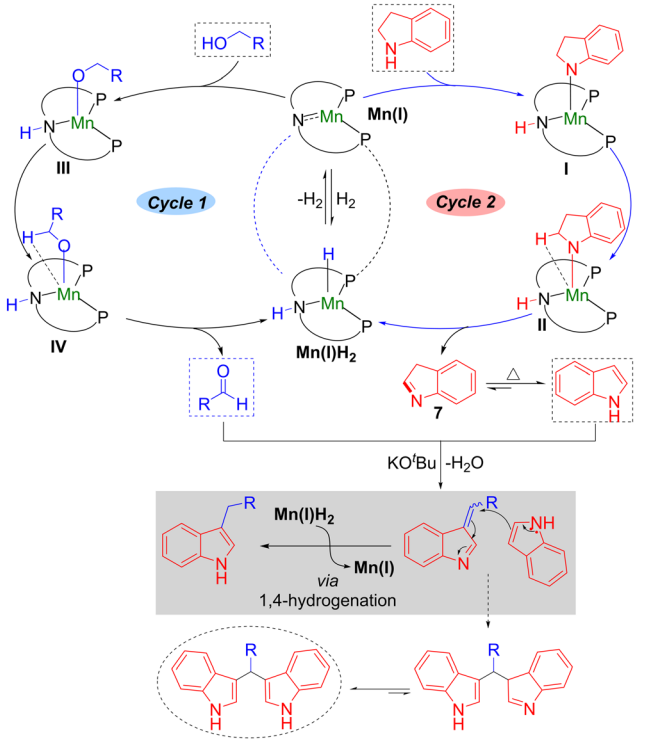


Fig. 2 Kinetic profiles of (left) [**Mn-2**]-catalyzed double AD/BH reaction of indoline (**1a**) and benzyl alcohol (**2a**) and (right) [**Mn-5**]-catalyzed AD/IBH reaction of indole and benzyl alcohol (**2a**).

well as GC-MS analysis. We believe that intermediate 7 undergoes selective 1,4-hydrogenation to give the CH-alkylated product (**3a**) under Mn(I)–PNP catalysis. In contrast, in the presence of cat.[**Mn-5**] the final (transfer)hydrogenation of the alkylideneindolenine (7) intermediate is slower than the Michael-type addition, and on further reaction with another indole moiety to provide the bis(indole)methane (BIM) as the sole product with the liberation of molecular hydrogen no formation of C3-alkylated indole was detected. The results show that the catalyst influences the CH alkylation of indoles under Mn catalysis. PNP–Mn(I) is very efficient for the borrowing hydrogenation (BH) reaction, while NNN–Mn(II) [**Mn-5**] has lower activity, and interrupted borrowing hydrogenation (IBH) reaction takes place. The liberation of hydrogen gas during the Mn(II)–NNN catalysis was qualitatively analyzed by GC. Thus, it can be concluded that both Mn(I)–PNN and Mn(II)–NNN catalytic systems behave antagonistically and follow BH and IBH strategies, respectively. Next, a reaction in the presence of 50 equiv. of mercury (Hg) did not affect the reaction, and we observed an 86% yield of the product. This result implies the homogeneous nature of the present catalytic systems. A similar reaction was performed with two equivalents of radical scavengers (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), and this experiment also shows that the reaction did not proceed through a single-electron path (Scheme 3d). It is worth mentioning that Marques and coworkers[20] proposed a radial coupling mechanism for the formation of BIM using a stoichiometric amount of K^{t}OBu under mediated conditions. To clarify if metal-mediated dehydrogenation is involved or not, we conducted kinetic studies on the reaction using different concentrations of NNN–Mn(II) [**Mn-5**]. The experimental results demonstrate that these one-pot tandem reactions are purely homogeneous, and the scope of the free radical mechanism can also be ruled out completely.

Finally, we performed kinetic experiments for both the catalytic systems. Accordingly, we monitored the reaction progress at a time interval of 6 hours and determined the concentration of substrate benzyl alcohol and indoline and the product by GC analysis. With the results, we have drawn a concentration *vs.* time plot, and the kinetic profile shows that this reaction depends on indoline/indole and benzyl alcohol concentration.

Based on several intermediate isolation control and labeling experiments, we have drawn a plausible catalytic cycle for the present Mn-catalyzed tandem AD/BH and AD/IBH strategies for CH alkylation of indoline (in the presence of [**Mn-2**]) or indole (Scheme 4). For better understanding, we have split the catalytic cycle into two sub-cycles, namely, cycle **1** and cycle **2**. Cycle **1** represents alcohol dehydrogenation, while cycle **2** represents indoline dehydrogenation. Catalytically active **Mn(I)** complex is formed upon treatment of **Mn-2** with a base (KO^{t}Bu). The first step of cycle **1** is the O–H bond activation of alcohol by **Mn(I)** to form manganese alkoxy intermediate **III**. This intermediate closely holds the β-proton of the alkoxide group through β-agostic interaction. Finally, β-hydride elimination eliminates aldehyde and generates manganese hydride complex **Mn(I)H$_2$**. In cycle **2**, the N–H bond activation of indoline by the **Mn(I)** complex generates imido manganese intermediate **I**. This intermediate exhibits an intramolecular β-agostic interaction,[21] and we mostly believe intermediate **II** will be generated. Intermediate **II** undergoes β-hydride elimination to generate a cyclic imine type intermediate (**IM-1**)[22] and manganese hydride **Mn(I)H$_2$** complex. Indeed, the active **Mn(I)** complex and **Mn(I)H$_2$** complex will be in equilibrium. The cyclic imine intermediate (7) undergoes aromaticity-driven tautomerization at a relatively high temperature to produce indole.[23] Subsequently, a base-mediated condensation reaction of indole with an aldehyde formed a



Scheme 4 A plausible mechanism for Mn(I)-catalyzed double dehydrogenative coupling of indolines with alcohols.

1,3-unsaturated intermediate (7). Finally, this alkylideneindolenine intermediate is selectively 1,4-hydrogenated with the aid of **Mn(I)H_2** to give the desired product, C3-alkylated indole. In contrast, in the case of Mn(II)–NNN catalysis (*i.e.* cat.[**Mn-5**]), the final (transfer) hydrogenation of the alkylideneindolenine (7) intermediate is slower than the Michael-type nucleophilic addition, and hence, further reaction with another indole moiety is required to provide the BIMs. Notably, the condensation of indole with benzaldehyde under Mn(III)–NNN catalysis was found to be fast, and a similar rate was observed when the reaction was performed with only KO^{t}Bu (see the ESI†). This result suggests that the Mn(II)–NNN catalyst is playing a key role in the initial dehydrogenation of alcohol to give the corresponding aldehyde, while KO^{t}Bu catalyzes the condensation of indole with *in situ* formed aldehyde, giving intermediate 7, and finally yields the BIMs.

Conclusions

In conclusion, we disclose judiciously chosen molecularly defined manganese complexes for the catalytic CH alkylation of indole/indolines with alcohols. The basic features of the present reaction are generality, selectivity, and wide substrate scope. A chemodivergence in the present CH alkylation is achieved through catalyst control. By use of a single-site PNP–Mn(I) complex, tandem double dehydrogenative CH alkylation of indoles is observed. Antagonistically, an NNN–Mn(II)-based catalyst system provides a diverse range of bis(indolyl)methanes (BIMs) *via* interrupted borrowing hydrogen. The present Mn catalysis was successfully applied for the sustainable, scalable, and benign synthesis of several life science molecules (vibrindole A, turbomycin B alkaloid, and antileukemic and anticancer agents) and natural products (gramine, dipterine, *etc.*).

Author contributions

AM and EB conceived and designed the project. AM performed the optimization studies, substrate scope, and mechanistic studies. RK and AKS helped in the substrate scope and mechanistic studies. AM, MKS and EB wrote the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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