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Iron-Catalyzed Reductive Cyclization by Hydromagnesiation: A Modular Strategy Towards *N*-Heterocycles

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Abstract: *A reductive cyclization to prepare a variety of N-heterocycles, through the use of ortho-vinylanilides, is reported. The reaction is catalyzed by an inexpensive and bench-stable iron complex and generally occurs at ambient temperature. The transformation likely proceeds through hydromagnesiation of the vinyl group, and trapping of the in situ generated benzylic anion by an intramolecular electrophile to form the heterocycle. This iron-catalyzed strategy was shown to be broadly applicable and was utilized in the synthesis of substituted indoles, oxindoles and tetrahydrobenzoazepinoindolone derivatives. Mechanistic studies indicated that the reversibility of the hydride transfer step depends on the reactivity of the tethered electrophile. The synthetic utility of our approach was further demonstrated by the formal synthesis of a reported bioactive compound and a family of natural products.*

Introduction

The catalytic hydrometall(oid)ation of C–C multiple bonds is a powerful tool in organic chemistry due to the possibility to generate useful synthetic intermediates from simple substrates.[1] More specifically, catalytic transfer hydromagnesiations employing organomagnesium reagents represent an elegant example of shuttle catalysis,[2] and are particularly interesting because of the versatility of the resulting new organometallic compounds and the possibility to generate Grignard reagents not accessible by traditional methods.[3] However, the use of transfer hydromagnesiation remains largely underdeveloped, in part due to poor functional group tolerance and a narrow substrate scope.

In recent years, the development of earth-abundant first row transition metal catalysts to enable hydrometallation reactions has attracted significant attention.[4] Iron catalysts are of particular interest due to the high abundance, unique reactivity, low cost, and comparatively low toxicity of iron versus many other transition metals.[5] In this context, the iron-catalyzed hydromagnesiation of alkenes has experienced a renaissance over the last decade,[6] long after the early observations by Kochi.[7] A breakthrough in the field was the iron-catalyzed hydromagnesiation of styrenes reported by Thomas and co-workers, which typically proceeds with excellent branch-selectivity.[8] While subsequent work focused on unravelling the mechanism of the reaction,[9] limited work has been conducted to expand its synthetic applications towards known value-added products.[10] Furthermore, those reactions are conducted in a two-step fashion, with the electrophile being added after the hydromagnesiation step in order to prevent its direct reaction with the Grignard reagent. Hence, it often suffers from poor functional group compatibility, with only simple styrene derivatives being tolerated (Scheme 1 a).

Within our program focusing on the development of novel transition metal-catalyzed syntheses of pharmaceutically relevant indoles,[11] we became interested in applying the recently developed iron-catalyzed hydromagnesiation of styrenes to access indoles as well as other *N*-heterocycles (Scheme 1 b). Substituted *N*-heterocyclic scaffolds are important structural motifs found in numerous pharmaceuticals and natural products, with almost 90% of all heterocycles synthesized in pursuit of novel drug candidates containing at least one nitrogen heterocycle.[12] As such, methods for their de novo preparation without the need for late transition metals remain in high demand.[13]

We envisioned that the reactive benzylic anion generated in situ from a styrene derivative could be trapped rapidly with a tethered electrophile in a true one-operation process to prepare the desired cyclic compounds. Preliminary studies identified readily available amides as suitable electrophiles in the transformation (Scheme 1 b, top). It is noteworthy that a similar strategy for the synthesis of indoles from *ortho*-vinylanilides relying on an interrupted Kulinkovich reaction[15] was previously reported by Cha,[16] but was limited to a single example with poor selectivity and required a stoichiometric amount of titanium as well as a large excess of the organometallic reagent. A notable feature of our strategy is that only a sub-stoichiometric amount of the organomagnesium compound should be present at any given time in the reaction mixture, potentially resulting in an improved functional group tolerance in comparison to traditional hydromagnesiation methods. This claim assumes the Grignard reagent is consumed rapidly in a fast hydromagnesiation reaction, after which a rapid intramolecular trapping occurs.

Overall, the process can be described as an iron-catalyzed hydromagnesiation-initiated Madelung-type indole synthesis[17] and represents an anionic variant of the Fukuyama indole synthesis which employs similar substrates.[18] Furthermore, this strategy represents expedient access to various *N*-heterocyclic cores bearing a 3-methyl group, which are prevalent in various drug molecules[19] and bioactive natural

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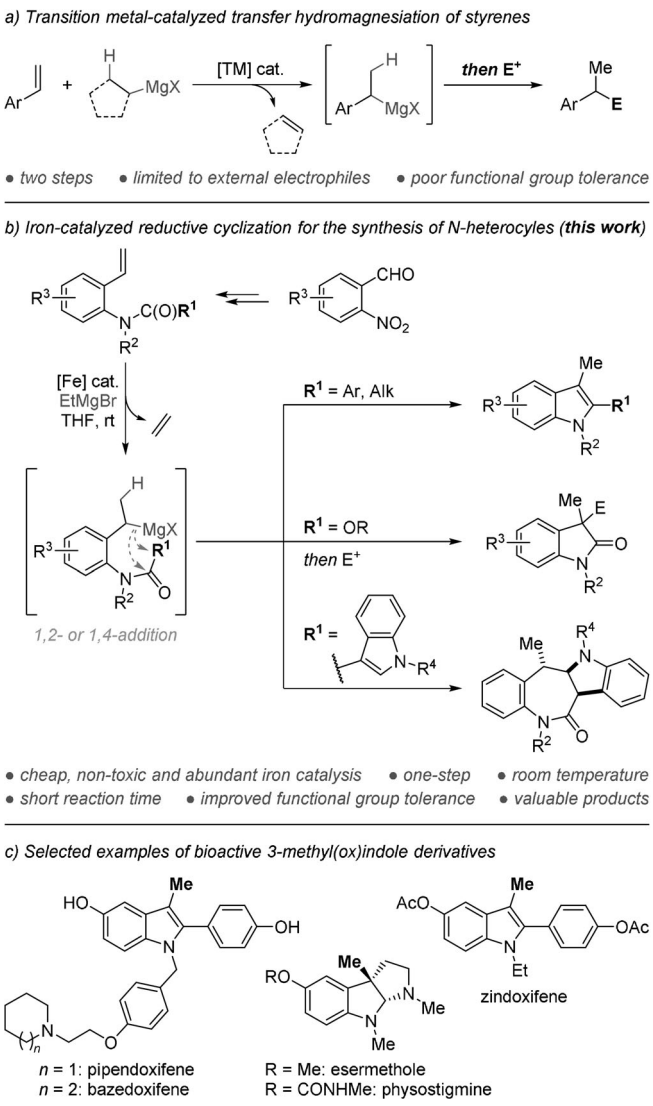


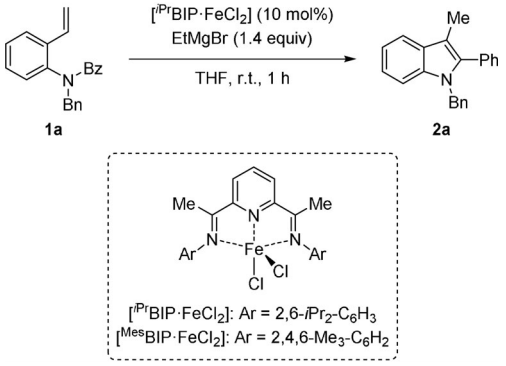
Scheme 1. a) General reaction scheme of the iron-catalyzed hydromagnesiation of styrenes and subsequent trapping with external electrophiles. b) Iron-catalyzed hydromagnesiation of styrenes and trapping with intermolecular electrophiles for the synthesis of *N*-heterocycles. c) Selected 3-methyl(ox)indole derivatives which display bioactivity.

products.[20] Improved synthetic pathways towards these important structures are warranted (Scheme 1c).

Results and Discussion

We initiated our study by investigating the reaction of benzamide **1a** with EtMgBr in the presence of the iron catalyst [$^{i\text{Pr}}$BIP·FeCl$_2$][21] (BIP = bis(imino)pyridine) employed by Thomas for the hydromagnesiation of styrenes[8] (Tables 1 and S-1[14]). The desired indole **2a** was obtained in high yield (entry 1). Control experiments confirmed $^{i\text{Pr}}$BIP and EtMgBr to be the optimal ligand and hydride source (entries 2–4 and Supporting Information). In contrast to previous reports, surprisingly poor results were obtained with TMEDA, possibly because the *ortho*-vinylanilide substrate is

Table 1: Optimization of the reaction parameters.[a]

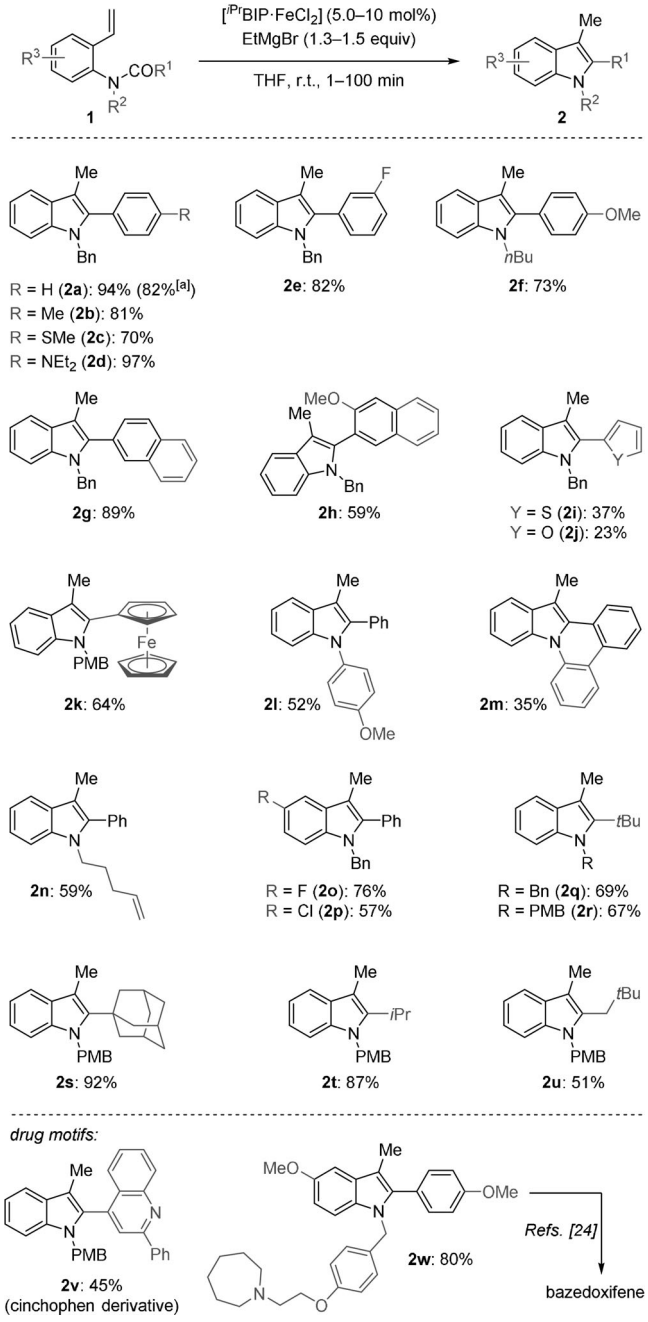


Entry	Deviation from standard conditions	Yield of **2a** [%]
1	none	>95
2	[$^{\text{Mes}}$BIP·FeCl$_2$] instead of [$^{i\text{Pr}}$BIP·FeCl$_2$]	73
3	FeCl$_2$ instead of [$^{i\text{Pr}}$BIP·FeCl$_2$]	19
4	FeCl$_2$ + TMEDA (20 mol%) instead of [$^{i\text{Pr}}$BIP·FeCl$_2$]	39
5	*i*PrMgCl instead of EtMgBr	30
6	Et$_2$Zn instead of EtMgBr	n.r.
7	[$^{i\text{Pr}}$BIP·FeCl$_2$] (5.0 mol%)	57
8	[$^{i\text{Pr}}$BIP·FeCl$_2$] (5.0 mol%), slow addition of EtMgBr	>95
9	[$^{i\text{Pr}}$BIP·FeCl$_2$] (5.0 mol%), slow addition of EtMgBr (1.3 equiv), 5 min reaction time	**94**[b]
10	[$^{i\text{Pr}}$BIP·FeCl$_2$] was omitted	0

[a] Reaction conditions: **1a** (0.20 mmol), [$^{i\text{Pr}}$BIP·FeCl$_2$] (10 mol%), EtMgBr (1.4 equiv, 3.0 M in Et$_2$O), THF (1.5 mL), r.t., 1 h. Yields determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [b] Isolated yield. n.r. = no reaction. For experimental details, see the Supporting Information.

less effective at stabilizing the iron(0) species, based on steric effects.[9a] The yield was considerably reduced when running the reaction at a lower catalyst loading (entry 7), presumably due to uncatalyzed side reactions between **1a** and the Grignard reagent,[14] but could be restored by the slow addition of EtMgBr (entry 8). Finally, the amount of EtMgBr could be reduced to 1.3 equiv and we found out that full conversion was reached within 5 min (entry 9). Additional control experiments confirmed the importance of the catalyst and the superiority of iron over other metals in the desired reaction (entry 10 and Supporting Information).

With the optimized reaction conditions in hand, we explored the versatility of the iron-catalyzed reductive cyclization in the synthesis of 1,2,3-trisubstituted indoles (Scheme 2). A broad range of benzamides **1** bearing electron-donating and withdrawing groups participated in the reaction, providing the corresponding 2-arylindoles **2** in good to excellent yields. Fortunately, even the very hindered 2-(3-methoxy-2-naphthyl)-indole **2h** was obtained in satisfactory yield. While 2-heteroarylindoles **2i,j** were only obtained in moderate yields, bulky ferrocenyl substituents are compatible with the transformation. Various alkyl, aryl and benzyl groups were tolerated as *N*-substituents of the 2-vinylanilides **1**. The reaction was found to be highly selective for styrene derivatives as additional non-conjugated double bonds were left entirely untouched. Additional functionalities on the



Scheme 2. Iron-catalyzed synthesis of indoles **2**. [a] 1.5 mmol scale. For experimental details, see the Supporting Information.

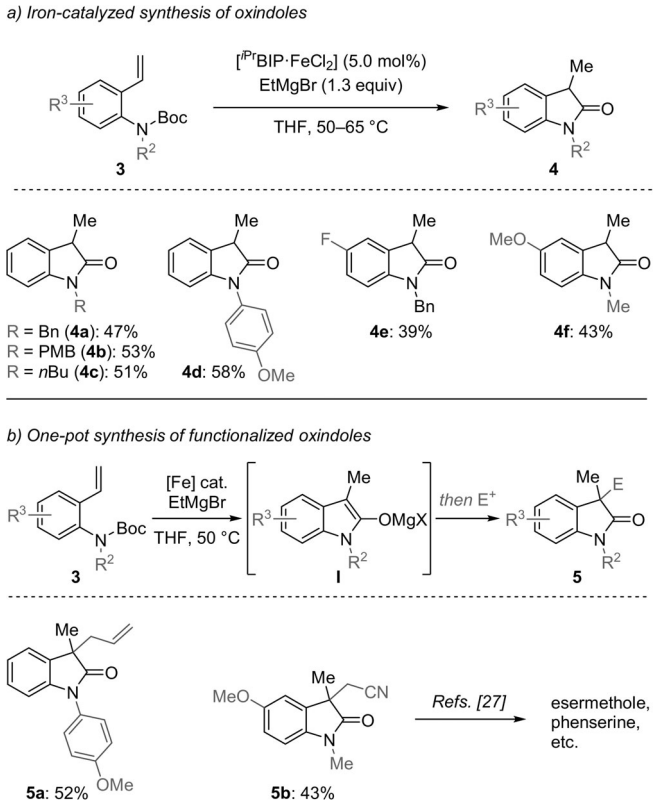
indole's benzene ring were well accommodated, including sensitive chloro substituents. It should be mentioned that the dechlorination of chloroarenes had previously been reported under similar conditions employing Grignard reagents and an iron catalyst,[10a,22] but this pathway could be prevented in our case presumably thanks to a very short reaction time and fast intramolecular trapping of reactive intermediates. Unfortunately, more reactive electrophiles were not tolerated.[14]

The transformation was not limited to the preparation of 2-arylindoles. Indeed, 1,2,3-trisubstituted indoles bearing primary, secondary as well as tertiary alkyl groups at the C2 position were obtained in good to excellent yields, including the sterically crowded product with an adamantyl group between two other substituents, **2s**.

Finally, the utility of the methodology was further illustrated by the facile synthesis and modification of drug motifs. Amide **1v**, derived from the analgesic drug cinchophen,[23] was submitted to the reaction conditions to afford indole **2v**. Moreover, an expedient formal synthesis of the antiosteoporotic drug bazedoxifene was realized. Its dimethyl ether **2w**, which has been reported as the final intermediate in several synthetic routes towards the drug,[24] was obtained in 80% yield through this iron-catalyzed reductive cyclization strategy.

Furthermore, our approach could be expanded beyond the synthesis of diversely decorated indoles. In keeping with our interest in the development of metal-catalyzed approaches toward the oxindole core,[25] we attempted to apply the methodology to the synthesis of 3-methyloxindoles **4**. The latter could be prepared by submitting carbamates **3** to the reaction conditions (Scheme 3a). In comparison to indoles, higher temperatures and increased reaction times were needed to obtain the oxindole products **4** in fair yields. It should be noted that a related strategy was previously described by Taguchi, but was a non-catalyzed process requiring excess pre-formed Negishi reagent.[26]

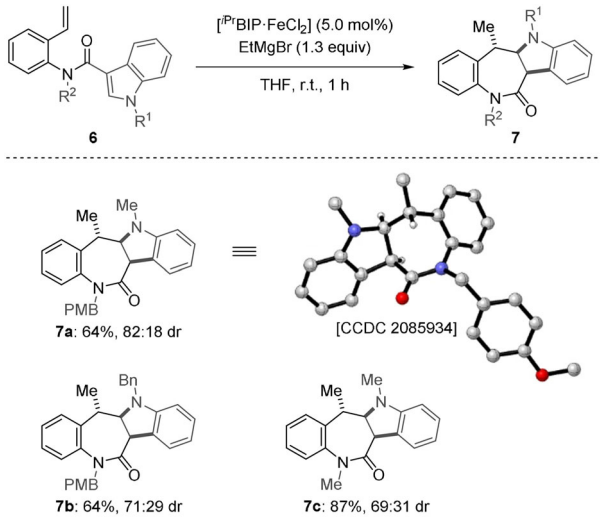
Additionally, the putative intermediate **I** could be trapped with external electrophiles in a one-pot process to access oxindoles bearing all-carbon quaternary centers (Scheme 3b). It is noteworthy that this process represents a formal 1,1-dicarbofunctionalization of the styrene moiety.



Scheme 3. Iron-catalyzed synthesis of oxindoles **4** and **5**. For experimental details, see the Supporting Information.

The synthetic utility of the transformation was demonstrated by the expedient preparation of **5b**, an advanced intermediate of the synthesis of both enantiomers of esermethole and other related bioactive alkaloids.[27]

Finally, the iron-catalyzed reductive cyclization strategy was applied to the synthesis of the novel polycyclic tetrahydrobenzoazepinoindolone scaffold **7** in good yield and moderate diastereoselectivity (Scheme 4). The connectivity



Scheme 4. Iron-catalyzed synthesis of tetrahydrobenzoazepinoindolones **7**.

and relative stereochemistry of product **7a** were unambiguously confirmed by X-ray diffraction analysis.[28] The reaction seemingly proceeds through an intramolecular dearomative[29] 1,4-addition of the in situ generated benzylic anion into the indole-3-carboxamide to yield *cis*-indoline **7**. It is notable that this iron-catalyzed strategy enables the selective hydromagnesiation across the styrene, utilizing the α,β-unsaturated amide as a terminating electrophile. This result is in contrast with a previous report which describes the 1,4-conjugate addition of Grignard reagents across related indole scaffolds.[30]

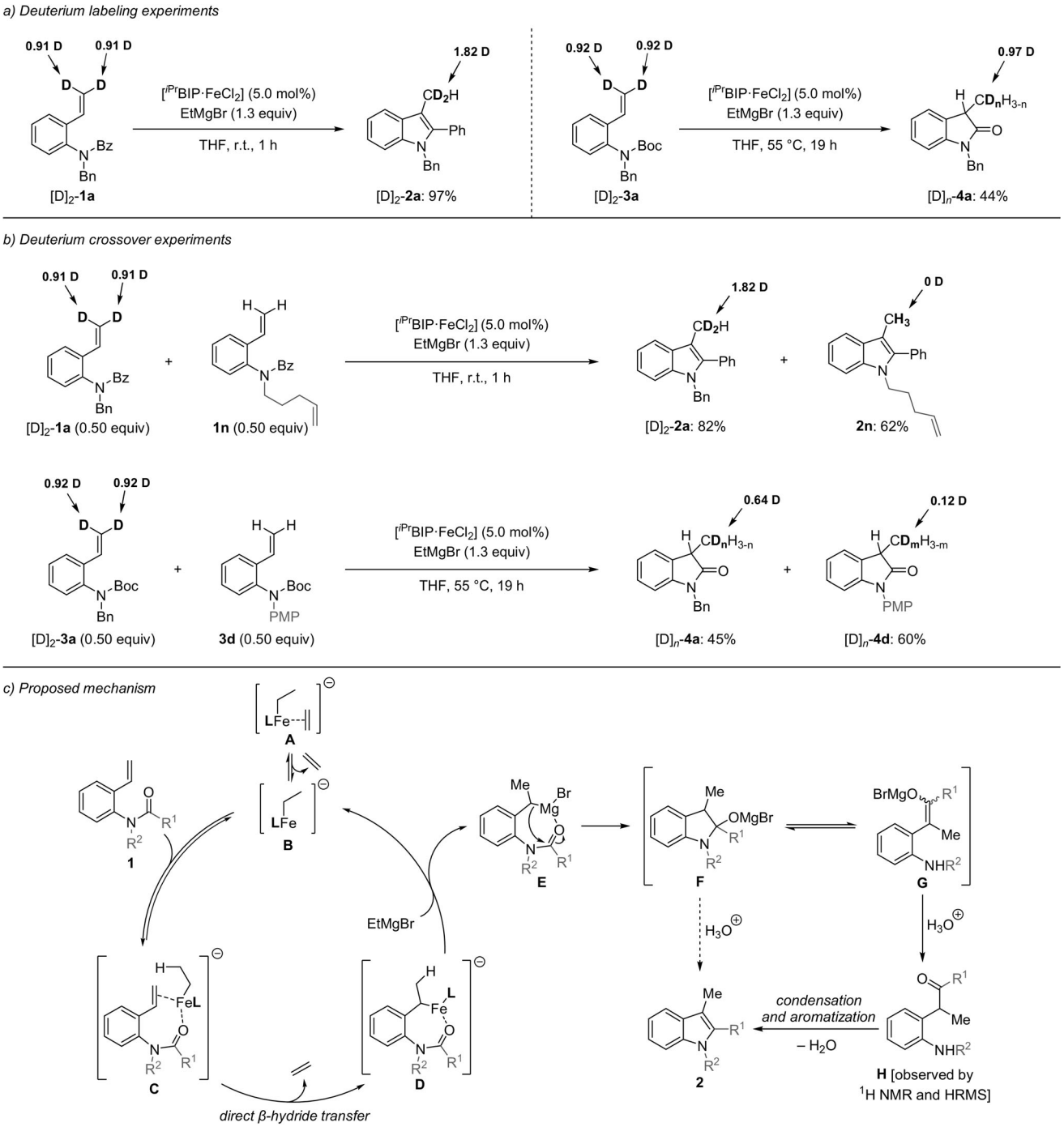
Given the unique features and versatility of this iron-catalyzed reductive cyclization, studies to probe the mechanism were undertaken. To this end, reactions with isotopically labeled *ortho*-vinylanilides were performed (Scheme 5). A complete and selective deuterium transfer to the 3-methyl group of indole $[D]_2$-**2a** was observed when benzamide $[D]_2$-**1a** was submitted to the reaction conditions (Scheme 5a, left). Crossover experiments were conducted, and no deuterium exchange was detected in the products of a reaction with substrates $[D]_2$-**1a** and **1n** or **1d** (Scheme 5b, top and Supporting Information). In contrast, a reaction with carbamate $[D]_2$-**3a** delivered oxindole $[D]_n$-**4a** as a mixture of isotopologues with an overall reduced content of deuterium (Scheme 5a, right). The loss of deuterium content can be attributed to H/D exchange with the Grignard reagent.[14] Furthermore, a deuterium crossover was observed in a reaction with carbamates $[D]_2$-**3a** and **3d** (Scheme 5b, bottom). These findings can be explained by a reversible hydride transfer, with the in situ generated benzylic anion serving as a hydride source in the hydromagnesiation of another molecule of the substrate rather than EtMgBr. These observations are in agreement with a recent mechanistic study by Neidig and Thomas who proposed the iron-catalyzed hydromagnesiation of styrenes to be reversible.[9b] On the other hand, the absence of H/D scrambling or deuterium crossover in the case of the synthesis of indoles **2** can be rationalized by a fast trapping of the in situ generated benzylic anion with the more reactive amide, resulting in an irreversible hydromagnesiation step.

On the basis of our results and literature precedent,[9] a plausible mechanism of the indole synthesis is depicted in Scheme 5c. An initial branch-selective iron-catalyzed hydromagnesiation delivers intermediate **E**. The in situ generated benzylic anion can then attack the amide moiety, yielding species **F** or **G**. According to control experiments,[14] this step seems to be a direct Grignard reaction not requiring the iron catalyst. Finally, aqueous workup generates intermediate **H**, which can readily undergo imine condensation and aromatization to provide the indole product **2**. It is noteworthy that in the case of the sterically crowded indole **2s**, intermediate **H** (**S-2**) was sufficiently stable to be observed by ^{1}H NMR and HRMS analysis of the crude product.[14] However, a mechanism involving the protonation of intermediate **F** cannot be fully excluded. Intermediates related to both **F** and **H** have previously been proposed or observed as intermediates in a related, multi-step, indole synthesis.[31]

Finally, the synthetic versatility of the indole products **2** was explored (Scheme 6). While the reaction remains so far limited to the preparation of 3-methylindoles, the methyl substituent can readily be converted to other functionalities. Indeed, aldehyde **8** was easily prepared from **2a** by oxidation with MnO_2, and the resulting formyl group can be removed[32] or employed as a versatile handle for further downstream derivatization.

Conclusion

In conclusion, we report a reductive cyclization for the expedient synthesis of sterically congested 1,2,3-trisubstituted indoles, and related *N*-heterocycles. The transformation, which is catalyzed by an inexpensive bench-stable iron complex, proceeds at ambient temperature with ample substrate scope. The fast intramolecular trapping of the in situ generated benzylic anion resulted in a short reaction time and an improved functional group tolerance in comparison to other hydromagnesiation reactions. Sensitive chlorides and amides are tolerated. This strategy also provides a conceptually innovative approach towards the one-pot synthesis of oxindoles with all-carbon quaternary centers and a novel polycyclic tetrahydrobenzoazepinoindolone scaffold. Preliminary mechanistic studies indicated that the reversibility of the hydride transfer step depends on the tethered electrophile. Finally, the applicability of the transformation was demonstrated by various derivatizations of the obtained indole products and the formal syntheses of an FDA-approved drug and several bioactive natural products. Further applications



Scheme 5. Reactions with isotopically labeled substrates and proposed mechanism. For experimental details, see the Supporting Information.

of hydromagnesiation-initiated cascade reactions are under way in our laboratory.

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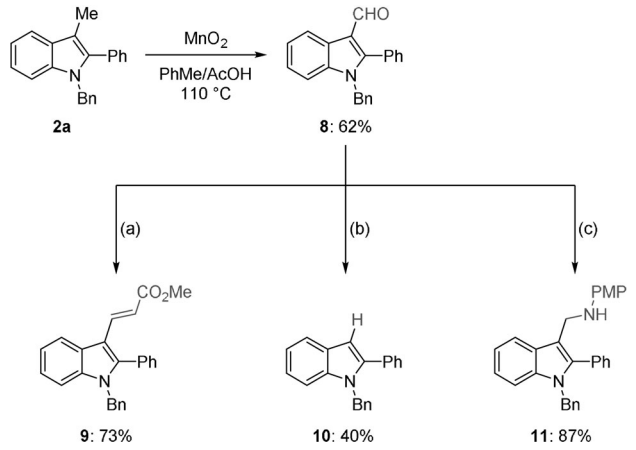
Conflict of Interest

The authors declare no conflict of interest.



Scheme 6. Product diversification. a) Ph_3PCHCO_2Me, PhMe, reflux. b) $Pd(OAc)_2$ (16 mol%), K_2CO_3, 4 Å MS, EtOAc, 150°C. c) *p*-Anisidine, $NaBH(OAc)_3$, AcOH, DCE, r.t. PMP = *para*-methoxyphenyl.

Keywords: hydromagnesiation · indole · iron catalysis · oxindole · reductive cyclization

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Research Articles

Synthetic Methods

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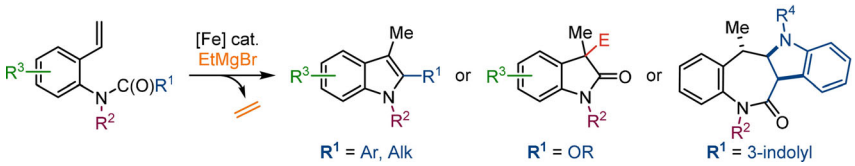
Iron-Catalyzed Reductive Cyclization by Hydromagnesiation: A Modular Strategy Towards *N*-Heterocycles



An iron-catalyzed reductive cyclization of 2-vinylanilides to prepare a variety of *N*-heterocycles is reported. The reaction, which usually occurs at room temperature over a short reaction time, employs an inexpensive and bench-stable iron catalyst and EtMgBr as a hydride source. The breadth of this strategy was demonstrated by the synthesis of densely substituted indoles, oxindoles and novel tetrahydrobenzoazepinoindolones, as well as the application towards the formal syntheses of bioactive compounds.