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Synthesis of 7-azabicyclo[4.3.1]decane ring system from tricarbonyl(tropone)iron via intramolecular Heck reactions

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Abstract

The 7-azabicyclo[4.3.1]decane ring system, common to a number of biologically active alkaloids, was accessed from tropone (via its η^4-diene complex with $Fe(CO)_3$) in a short sequence of steps: 1) nucleophilic amine addition and subsequent Boc-protection; 2) photochemical demetallation of the iron complex; 3) intramolecular Heck reaction. Minor modifications to the protocol enabled access to the related 2-azabicyclo[4.4.1]undecane and 8-azabicyclo[5.3.0]decane ring systems, albeit in lower yield.

Keywords

alkaloids; Heck reaction; azabicycles; tropone; iron complex

Introduction

Azapolycycles are embedded within numerous biologically active alkaloids [1] and pharmaceuticals [2]. As such, novel approaches to the synthesis of these motifs have attracted considerable interest. Synthesis of azapolycycles containing a seven-membered carbocyclic ring is particularly challenging compared to comparable skeletons containing only five- or six-membered rings [3]. Thus, comparatively few general methods exist for accessing these scaffolds, even though they are found within a number of biologically active alkaloids. We recently demonstrated that the readily available, bench-stable tricarbonyl(tropone)iron complex [4] (**1**, Scheme 1) could serve as a precursor to the previously unreported 2-azatricyclo[4.3.2.0^{4,9}]undecane ring system[5] (**3**, Scheme 1). We sought to demonstrate that this iron complex could serve as a common, versatile building block for additional azapolycyclic skeletons.
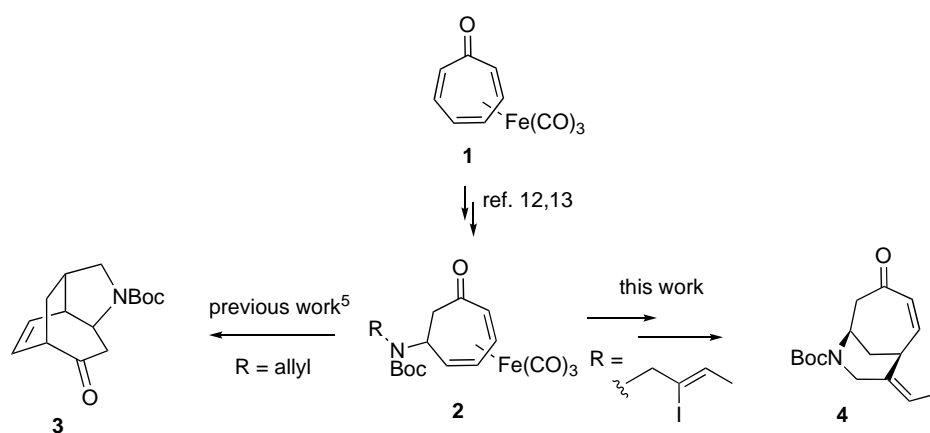
Scheme 1: Synthesis of diverse azapolycycles from iron complex **2** derived from tricarbonyl(tropone)iron.

The 7-azabicyclo[4.3.1]decane ring system is found within several complex alkaloids, including daphnicyclidin A [6-9] and ervitsine [10, 11] (Figure 1). We reasoned that, with an appropriately functionalized amine side chain and properly disposed unsaturation on the seven-membered ring, an intramolecular Heck reaction could give rise to this skeleton (**4**) in just a

few steps from tricarbonyl(tropone)iron (Scheme 1). Herein, we report our successful efforts to access this bridged bicyclic ring system.

daphnicyclidin A

ervitsine
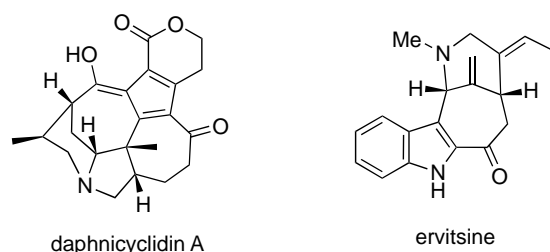
Figure 1: Complex alkaloids containing the 7-azabicyclo[4.3.1]decane ring system.

Results and Discussion

As shown in Scheme 2, synthesis of the requisite Heck reaction precursor began with addition of the known allylic amine **5** to tricarbonyl(tropone)iron, immediately followed by Boc-protection of the crude, resulting secondary amine according to our previously described, solvent-free protocol [12, 13]. The resulting iron complex (**6**) was demetallated upon irradiation with UV light [14] to give the deconjugated olefin **7**.
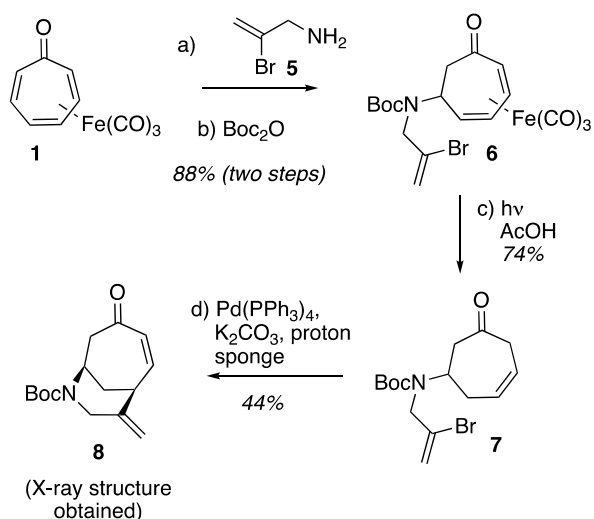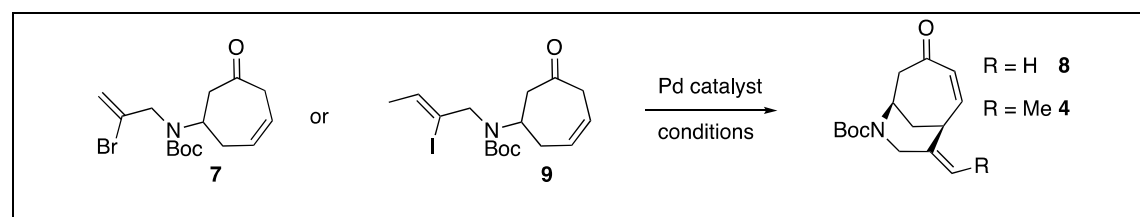
Scheme 2: Synthesis of bridged bicycle **8**. Reagents and conditions: a) neat (5 equiv. **5**), 24 h; b) Boc$_2$O, NaHCO$_3$, EtOH, ultrasound, 1 h, 88% (two steps); c) AcOH, hν (360 nm), 6 h, 74%; d) Pd(PPh$_3$)$_4$, K$_2$CO$_3$, proton sponge, PhMe, 110 ℃, 4 h, 44%

We then hoped to forge the desired bicycle **8** via a 6-*exo-trig* Heck cyclization, drawing on the vast body of knowledge built from many synthetic campaigns towards the *Strychnos*

alkaloids [15]. Several combinations of palladium catalyst, base, and other additives were applied to our system (see Table 1, entries 1-4). Reaction conditions such as those deployed to great effect by Rawal [16] (entry 2) and Vanderwal [17] (entry 3) in the synthesis of other bridged azapolycycles gave poor yields when applied to vinyl bromide **7**. The best result was obtained using the combination of Pd(PPh$_3$)$_4$, K$_2$CO$_3$, and proton sponge in refluxing toluene [18, 19]. Although this catalyst system proved best among those screened, yields remained modest (44%). Nevertheless, X-ray quality crystals of **8** could be obtained, which provided confirmation of the desired structure (CCDC No. 2263675).

Table 1: Screening of conditions for intramolecular Heck reaction of vinyl halides **7** and **9**

Entry	Substrate	Conditions	Yield (%)
1	**7**	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, dioxane, 120 °C, 4 h	15
2	**7**	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, MeCN, 80 °C, 2 h	15
3	**7**	Pd(PPh$_3$)$_4$, PMP, MeCN, 70 °C, 4 h	17
4	**7**	Pd(PPh$_3$)$_4$, proton sponge, K$_2$CO$_3$, PhMe, 110 °C, 4.5 h	44
5	**9**	see entry 4	45
6	**9**	Pd(OAc)$_2$, K$_2$CO$_3$, n-Bu$_4$NCl, DMF, 70 °C, 4 h	7
7	**9**	Pd(PPh$_3$)$_4$, K$_3$PO$_4$, PhOH, Et$_3$N, PhMe, 110 °C, 4 h	76
8	**7**	Pd(PPh$_3$)$_4$, K$_3$PO$_4$, PhOH, Et$_3$N, PhMe, 110 °C, 2 h	42

While searching for methods to improve the yield of our desired azabicycle, we came across the observation of Andrade and Kokkonda that vinylic halides with the same substitution pattern as **7** tend to give poor yields in similar intramolecular Heck reactions [20]. Moreover, it

was found that substrates on which the halide is *cis* to an additional methyl substituent (used to forge the ethylidene-substituted polycycle common to many alkaloids) often give superior yields for otherwise identical Heck reactions. Thus, iodoamine **11** (Scheme 3) was synthesized (see Supporting Information File 1) to evaluate this finding in the context of our system.
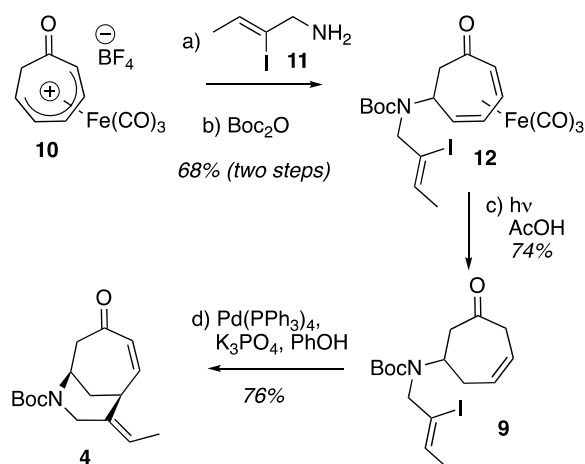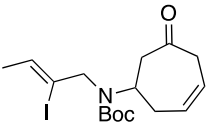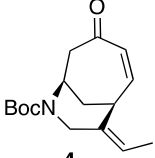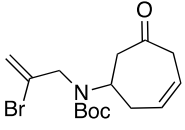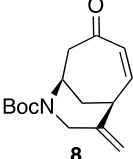

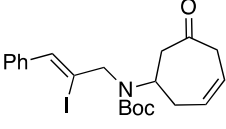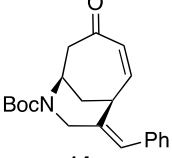**Scheme 3.** Optimized synthesis of bridged azabicycle **4**. Reagents and conditions: a) **11** (2 equiv.), EtOAc, 23 ºC, 1 h; 2) Boc$_2$O, NaHCO$_3$, EtOH, ultrasound, 23 ºC, 1 h, 68% (two steps); c) AcOH, hv (360 nm), 23 ºC, 6 h, 74%; d) Pd(PPh$_3$)$_4$, K$_2$CO$_3$, PhOH, Et$_3$N, PhMe, 110 ºC, 4 h, 76%.

Surprisingly, subjection of **9** to the same conditions that proved optimal for vinyl bromide **7** resulted in formation of the expected product **4**, but with essentially no improvement in yield (Table 1, entry 5). Searching anew for an improved set of reaction conditions, we subjected **9** to a "ligandless" palladium catalyst (Jeffery conditions) [16], which provided a very low yield (entry 6). However, we had better success when we adapted conditions developed by Bennasar, which elevated the yield to 76% (entry 7) [10]. It has been postulated [21] that phenoxide is capable of stabilizing one or more of the intermediate Pd complexes, which may account for the higher yield. Interestingly, applying these conditions to the vinyl bromide **7** resulted in no improvement over the previously optimized conditions (entry 8).

Having established an efficient route to our desired azabicycle from tropone, we sought to employ additional amine nucleophiles bearing pendant vinyl iodides to access several

analogs of **4** (see Supporting Information File 1 for amine syntheses). These amines were each carried through the protocol outlined in Scheme 3 to arrive at the deconjugated olefin substrates shown in Table 2. The cinnamylamine derivative **13** underwent the Heck cyclization in 50% yield, while the prenylamine derivative **15** proceeded to give **16** in 75% yield. These results suggest that these Heck cyclizations are quite sensitive to the identity of the alkene substituent that is *cis* to the halogen. We were also interested in engaging vinyl iodide **17** in a 7-*exo*-trig cyclization to form **18**. *Z*-iodoalkene **17** appeared to react cleanly according to TLC analysis, but the isolated yield of the intramolecular Heck product was low, perhaps due to instability of one of the intermediate palladium complexes and/or a slow olefin insertion step. Moreover, the product was obtained as an inseparable mixture of the allylic carbamate **18** and the isomeric enecarbamate **19** (the precise product ratio was variable across several trials, largely due to silica gel facilitating the equilibration of **18** and **19**).

Table 2: Intramolecular Heck reactions of various substituted vinyl halides[a]

Substrate	Product	Yield (%)
9	**4**	76
7	**8**	42
13	**14**	50

15	**16**	75
17	**18**　**19**	15[b]
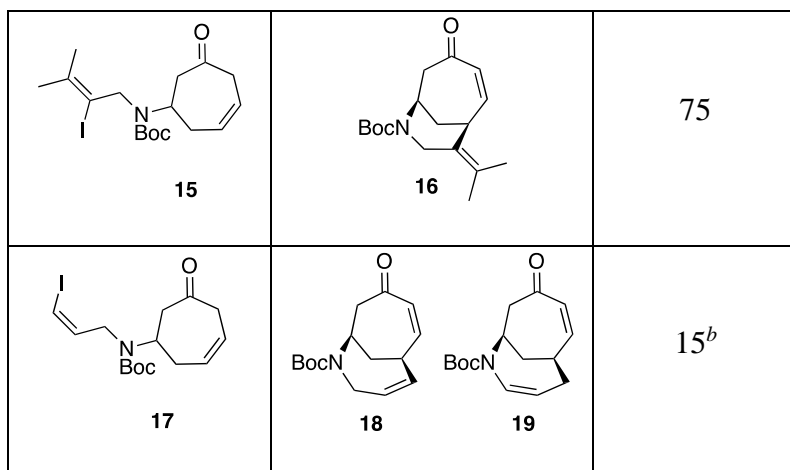
[a]reaction conditions: Pd(PPh$_3$)$_4$, K$_3$PO$_4$, PhOH, Et$_3$N, PhMe, 110 °C; [b]combined yield of **18** and **19**

Having successfully accessed bridged azabicycle **4** along with several analogs from tropone, we wondered whether a slight modification to the Heck reaction substrate would afford access to an alternative bicyclic system. Our previous work [12] had shown that *aza*-Michael adducts of tricarbonyl(tropone)iron undergo clean oxidative demetallation with cerium ammonium nitrate to give the corresponding dienones. We postulated that dienone **20** (Scheme 4a) could undergo a reductive, 5-*exo-trig* Heck cyclization to give the densely functionalized fused system **23** via Pd π-allyl intermediates **21** and **22**. The oxidative demetallation of vinyl iodide **12** proceeded without incident to give conjugated dienone **20** in 95% yield (Scheme 4b).
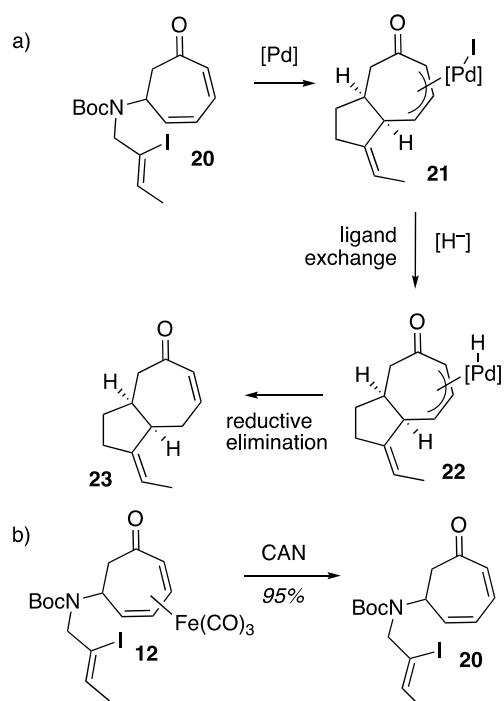
Scheme 4: a) Envisioned reductive Heck reaction for synthesis of fused bicycle **23**; b) Oxidative demetallation; Reagents and conditions: CAN (3 equiv.), MeOH/acetone, 0 ºC, 95%

Our efforts towards effecting this reductive Heck cyclization drew inspiration from the work of Grigg [22], in which sodium formate serves as a hydride donor. Although the conditions reported by Grigg appeared, in our hands, to afford some of the desired reductive Heck product, we found this product was often formed alongside one or more other products, not all of whose structures could be identified (one of these recurring products appeared to be conjugated triene **24**, Scheme 5a). Moreover, we found the outcomes of these reactions to be highly variable in terms of yields and product ratios. We thought that perhaps using a greater excess of sodium formate could facilitate the isolation of a single product (**23**), but this proved not to be the case, as similar results were obtained when using a slight excess of the reductant. Interestingly, these reactions appeared to give different products among those mentioned above upon minor changes to the reaction conditions.
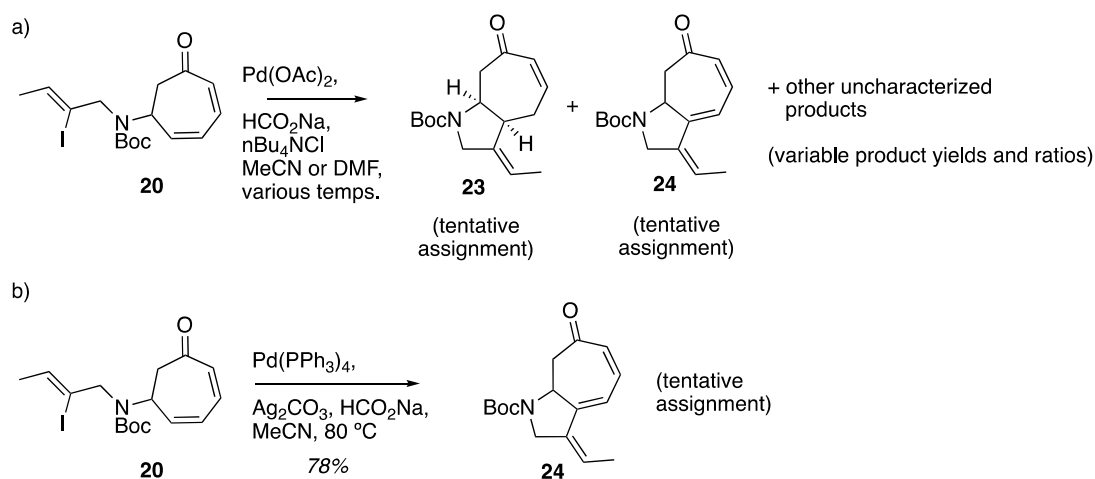
Scheme 5: a) Attempted reductive Heck reactions of dienone **20**; b) Redox neutral Heck reaction of dienone **20** facilitated by Ag_2CO_3.

In search of more reproducible reaction conditions, we attempted the Heck reaction with silver carbonate as an additive (Scheme 5b) with hopes that Ag(I) could facilitate exchange of the iodide ligand for a hydride in the intermediate palladium complex. Unexpectedly, these conditions appeared to cleanly afford the triene **24** as the sole product as suggested by TLC and

NMR analysis of the crude product mixture. Though this Heck reaction does not formally proceed through a reductive pathway, we found that the reaction failed if sodium formate was omitted. It is unclear what role this additive is playing in the reaction, nor is it clear how silver carbonate allows the formation of the observed triene to the exclusion of all other products observed previously. Although somewhat puzzling, this result demonstrates that structurally diverse azabicycles can be readily accessed with only minor changes to the reaction conditions. Unfortunately, the crude triene proved highly sensitive to any method of purification attempted, be it chromatography on Et$_3$N-deactivated silica gel, alumina, or similar stationary phases. Specifically, the exocyclic olefin proved highly susceptible to *E/Z* isomerization under these conditions, and an additional compound also began to form upon attempted chromatography whose structure could not be identified. Prolonged exposure of the crude material to silica gel in an attempt to form this unknown product exclusively were unsuccessful, leading only to an uncharacterizable mixture. As such, triene **24** could not be fully characterized.

Conclusion

In conclusion, we have shown that bridged azabicycles common to a number of alkaloid natural products can be accessed from commercially available tropone in as little as five steps: 1) formation of tricarbonyl(tropone)iron; 2) *aza*-Michael addition; 3) amine protection; 4) photodemetallation; 5) intramolecular Heck reaction (two steps—*aza*-Michael addition and amine protection–can potentially take place in one pot). We have shown that this protocol can be applied to the synthesis of several analogs bearing different substitution patterns on the alkene. In addition, we have shown that the same protected *aza*-Michael adducts can be *oxidatively* demetallated and that the resulting conjugated dienones can undergo Heck cyclizations to form *fused* azabicycles, though these fused products proved challenging to isolate. The structural diversity that can be readily obtained utilizing this chemistry underscores

the versatility of tropone as a synthetic building block for accessing functionalized azapolycycles containing seven-membered rings.

Supporting Information

Supporting Information File 1:

File Name: Shoemaker_BJOC_experimental

File Format: .docx

Title: Experimental procedures for all new compounds and summary of X-ray structure data for compound **8**

Supporting Information File 2:

File Name: Shoemaker_BJOC_spectra

File Format: .pdf

Title: Copies of ^{1}H and ^{13}C NMR spectra of all purified novel compounds

Supporting Information File 3:

File Name: DGbicyclicNboc_1_0m.cif

File Format: .cif

Title: CIF of X-ray structure for compound **8**

Acknowledgements

Funding

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