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Domino Heck−Aza-Michael Reactions: Efficient Access to 1-Substituted Tetrahydro-β-carbolines

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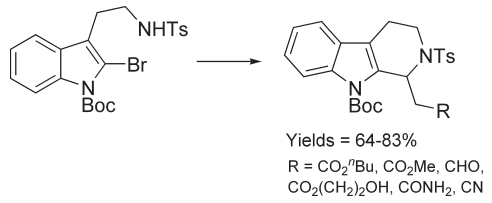

A simple and efficient palladium-catalyzed domino reaction for the synthesis of a series of C1-substituted tetrahydro-β-carbolines is described. This domino process involves a Heck reaction at the indole 2-position of a halogenated tryptamine precursor, followed by intramolecular aza-Michael addition.

Tetrahydro-β-carbolines (THβCs or tryptolines) substituted at the 1-position are central to a number of pharmaceutical targets with potential for the treatment of medical conditions including breast cancer, type-2 diabetes, and bacterial infections.[1] This ring system is prevalent in several more structurally complex natural products, including the secologanin-type terpenoid indole alkaloid ajmalicine (**1**) (Figure 1) and the antihypertensive agent reserpine (**2**).[1a,2] Biosynthetically, attaching a 3-(l-Δ′-pyrroliniumyl)propanal to this carboline ring system accesses the alkaloid elaeocarpidine (**3**) containing an additional indolizidine ring fragment.[3]

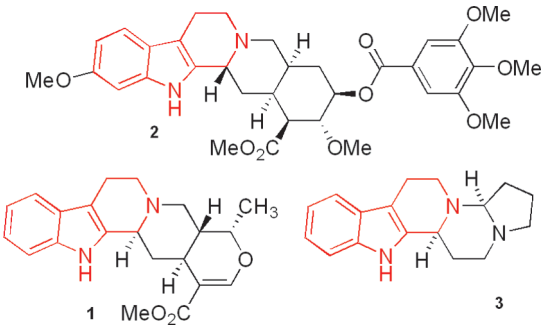

FIGURE 1. Natural products (**1**−**3**) containing the tetrahydro-β-carboline heterocyclic core.

Domino reactions are an attractive proposition for the modern synthetic chemist, generating a high level of molecular complexity in one efficient step.[4] A domino reaction is defined as "the execution of two or more bond-forming transformations under identical reaction conditions, in which the latter transformations take place at the functionalities formed by the preceding transformation."[4,5]

These reactions are appealing to industry and research laboratories because of their potential to minimize the use of solvents, reagents, time, and energy.[4] The more conceivable domino reactions are those where all transformations occur under similar reaction conditions, for example, where each of the steps are palladium-catalyzed.[5,6] The range of single-step reactions involving palladium catalysis has grown to the extent where palladium-mediated reactions are commonplace in most synthetic laboratories. Consequently, the number of palladium-mediated domino reactions has also increased over the past decade.[7] In spite of this increase, domino Heck−Michael methodology remains relatively underutilized, with limited examples in the literature.[8] Of those reported, only one details a domino Heck−aza-Michael process, used in the synthesis of benzo-fused sultams.[8c]

Due to their biological relevance, it is important that molecularly diverse THβCs are prepared containing multiple sites for further functionalization. Traditionally, C1-substituted THβCs are accessed through the acid-catalyzed Pictet−Spengler reaction between tryptamine and an appropriate aldehyde.[9] Alternatively, a four-step process involving a

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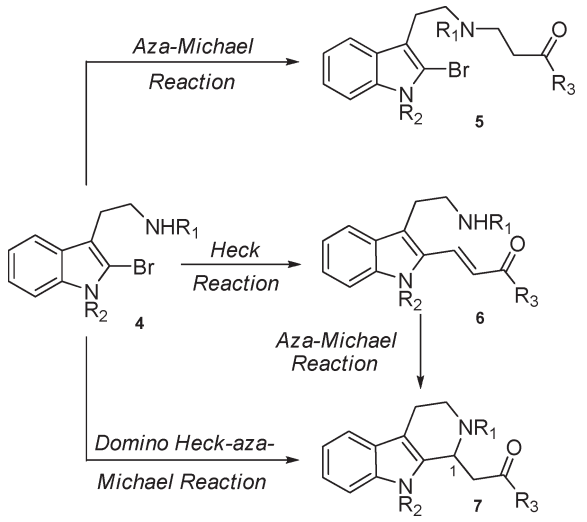
SCHEME 1. Single Step versus a Domino Process To Access THβCs



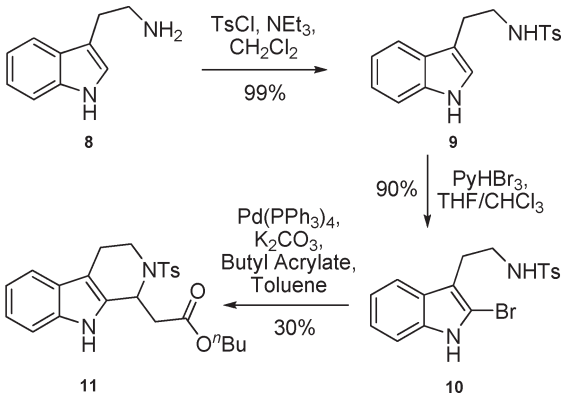
Bischler−Napieralski reaction to afford the dihydro-β-carboline and subsequent reduction is effective in producing specific THβCs.[10]

More recently, due to difficulties in the preparation and handling of the requisite aldehydes (for example, β-formyl esters[11]), modified Pictet−Spengler reactions have been developed using alternatives such as alkynoates[2a] and perhydro-1,3-heterocycles.[2c] To complement these existing methodologies, a domino Heck−aza-Michael reaction of a tryptamine derivative (such as compound 4, Scheme 1) was foreseen as an efficient method for introducing molecular diversity at C1 of the THβC scaffold. Using cheap and readily available acrylates under mild conditions, an orthogonally protected THβC scaffold containing multiple sites for further functionalization would be readily accessible.

The indole C2-position of tryptamine was considered ideal for further functionalization using a domino Heck−aza-Michael reaction (Scheme 1). Palladium-catalyzed cross-coupling of C2-halogenated indole compounds, namely, the Heck, Sonogashira, and Suzuki reactions, has been reported by our group and others.[12] As the Heck reaction regenerates the olefin functionality following *syn*-elimination and is reliably efficient with electron-deficient terminal alkenes, the potential exists for a second nucleophilic addition reaction. In this case, a 1,4-Michael addition should be suitable, depending on the nature of the tethered amine and if it reacts before or after the Heck reaction (an intra- vs intermolecular aza-Michael reaction; see Scheme 1).

As such, a domino Heck−aza-Michael transformation with an appropriately functionalized tryptamine was considered highly likely as both aza-Michael addition[13] and the Heck reaction[14] take place under mildly basic conditions. In this domino process, a new C−C and C−N bond would be created in sequence, at the same carbon atom.

SCHEME 2. Initial Attempts of the Domino Heck−Aza-Michael Reaction in the Synthesis of the Tetrahydro-β-carboline 11



Initially, several protecting groups (at R_1, Scheme 1) including *tert*-butoxycarbonyl, trifluoroacetate, tosyl, benzenesulfonyl, and 2-nitrobenzenesulfonyl were trialed to influence the acidity of the proton on the protected amine, tuning nucleophilicity at the tryptamine N10 nitrogen. During these preliminary investigations, the tosyl group was quickly identified as most suited to our domino system.[6b]

The tosyl protection of the primary amine within tryptamine (**8**) proceeded in quantitative yields to afford sulfonamide **9**. Similarly, bromination of the C2 position proceeded readily to give 2-bromoindole **10** in excellent yields (90%). Following preliminary treatment of the precursor **10** with $Pd(PPh_3)_4$, K_2CO_3 and butyl acrylate, the target tetrahydro-β-carboline **11** was isolated in a promising yield of 30% (Scheme 2).

The synthesis of carboline **11** from tryptamine (**8**) was achieved in three steps in a moderate overall yield of 27%. More importantly, this encouraging result confirmed that the domino Heck−aza-Michael reaction was applicable to this particular ring system. To improve the yield, three features of the domino Heck−aza-Michael reaction were identified for further optimization, namely, the Heck reaction, the nucleophilicity of the sulfonamide, and the degree of electron deficiency of the Michael acceptor. The Heck reaction, the initial step of this domino process, was optimized first, with the roles of the palladium catalyst, base, and the solvent investigated (Table 1).

The results from this investigation were consistent with previous reports of the Heck reaction at the indole 2-position,[12c,15] with $Pd(PPh_3)_4$ (10 mol %) providing the highest yields. Interestingly, the use of Na_2CO_3 (Table 1, entry 5) produced only the Heck adduct **12** in excellent yields, whereas K_2CO_3 facilitated the formation of the desired tetrahydro-β-carboline **11** (Scheme 2). Unfortunately, the highly reactive catalytic system pioneered by Fu[16] afforded only a moderate yield for the Heck product (Table 1, entry 3).

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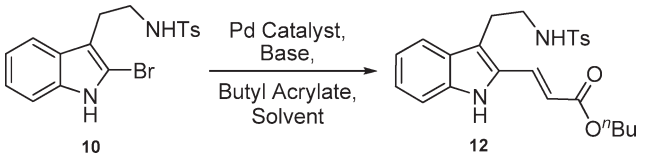
TABLE 1. Optimization of the Heck Transformation of Arylbromide 10



entry	catalyst (10 mol %)	base	solvent	yield (%)
1	$Pd(OAc)_2/PPh_3$[a]	NEt_3	toluene	22
2	$Pd_2(dba)_3/P(tBu)_3$[a]	NEt_3	toluene	43
3	$Pd_2(dba)_3/P(tBu)_3$[a]	Cy_2NMe	toluene	65
4	$Pd(PPh_3)_4$	NEt_3	toluene	39
5	$Pd(PPh_3)_4$	Na_2CO_3	toluene	99
6	$Pd(PPh_3)_4$	K_2CO_3	DMF	trace[b]
7	$Pd(PPh_3)_4$	K_2CO_3	MeCN	trace[b]
8	$Pd(PPh_3)_4$	K_2CO_3	dioxane	32
9	$Pd(PPh_3)_4$	CH_3CO_2Na	toluene	75

[a]Catalyst and ligand used in a 1:1 ratio. [b]Trace is $<10\%$ as determined by ^{1}H NMR.

With the Heck reaction proceeding in excellent yields, the second step in the domino sequence, the aza-Michael addition, was explored (Table 2).[17] A range of organic amines (i.e., NEt_3, DBU) and inorganic bases (i.e., Na_2CO_3, K_2CO_3, Cs_2CO_3) did not improve the domino transformation.

A range of solvents were also trialed to improve the $Pd(PPh_3)_4$, K_2CO_3 catalytic system; however, solvents more polar than toluene (MeCN, DMF, and dioxane, Table 2, entries 6–8) failed to increase the yield of the domino process with many of these increasing the propensity for the sulfonamide to undergo an initial 1,4-addition (to compound **5**, Scheme 1). In such cases, the relatively slow rate of the Heck reaction is secondary to the more reactive intermolecular aza-Michael addition.

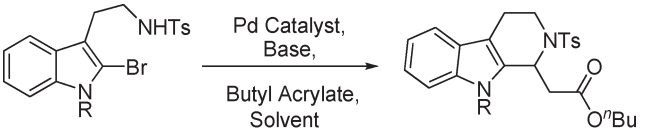
The addition of the phase transfer agent TBAC to improve the rate of key steps in the catalytic cycle (Table 2, entries 10 and 11) also failed to increase the yield of the domino process beyond 30%.[14,18] Alternatively, a change in the reactivity of the α,β-unsaturated moiety in the initial Heck adduct was envisaged through protection of the indole nitrogen. To our delight, this approach proved successful and the domino reaction using *N*-Boc indole **13a** produced the desired carboline **14a** in an excellent yield of 83% (Table 2, entry 14).

To further investigate the role of indole *N*-substitution on the domino process, two additional protecting groups were trialed (Table 2, entries 18 and 19). These substrates were reacted according to the previously identified conditions for the domino process, and a marked improvement in the yield of the desired tetrahydro-β-carbolines was observed.

The highest yields (up to 83%) for the domino process were obtained following the addition of $Pd(PPh_3)_4$ (10 mol %), alkene (1.1 equiv), and K_2CO_3 (3.0 equiv) to a sealed tube containing 2-bromoindole (1.0 equiv) in toluene (5 mL) that was subsequently stirred at 120 °C for 16 h. A simple purification protocol, including column chromatography, furnished the desired tetrahydro-β-carbolines. Reproducible yields for this domino process were obtained on various scales (ranging from 0.1 to 1.1 mmol).

To illustrate the versatility of this methodology, the domino Heck–aza-Michael reaction was repeated using a

TABLE 2. Optimization of the Domino Heck–Aza-Michael Reaction of Arylbromides



10 R = H
13a = Boc
13b = Bn
13c = Ts

11 R = H
14a = Boc
14b = Bn
14c = Ts

entry	substrate, product	catalyst (10 mol %)	base	solvent	yield (%)
1	**10**, **11**	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	0
2	**10**, **11**	$Pd(PPh_3)_4$	NEt_3	toluene	trace[a]
3	**10**, **11**	$Pd(PPh_3)_4$	DBU	toluene	trace[a]
4	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	toluene	30
5	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	toluene	30[b]
6	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	MeCN	trace[a]
7	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	DMF	trace[a]
8	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	dioxane	0
9	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	toluene	14[c]
10	**10**, **11**	$Pd(PPh_3)_4$	K_2CO_3	toluene	trace[a,d]
11	**10**, **11**	$Pd(PPh_3)_4$	Na_2CO_3	toluene	17[d]
12	**10**, **11**	$Pd_2(dba)_3/P(tBu)_3$[f]	NEt_3	toluene	trace[a]
13	**10**, **11**	$Pd_2(dba)_3/P(tBu)_3$[f]	Cy_2NMe	toluene	0
14	**13a**, **14a**	$Pd(PPh_3)_4$	K_2CO_3	toluene	83
15	**13a**, **14a**	$Pd(PPh_3)_4$	K_2CO_3	MeCN	trace[a]
16	**13a**, **14a**	$Pd(PPh_3)_4$	Na_2CO_3	toluene	27
17	**13a**, **14a**	$Pd(PPh_3)_4$	Na_2CO_3	toluene	86[e]
18	**13b**, **14b**	$Pd(PPh_3)_4$	K_2CO_3	toluene	54
19	**13c**, **14c**	$Pd(PPh_3)_4$	K_2CO_3	toluene	54

[a]Trace is $<10\%$ as determined by ^{1}H NMR. [b]Using 2 equiv of butyl acrylate. [c]Using 3 equiv of butyl acrylate also resulted in a large formation of only the aza-Michael product **5**. [d]Tetra-*n*-butylammonium chloride added to initial reaction mixture. [e]A one-pot process where tetra-*n*-butylammonium chloride was added to reaction mixture after 12 h at 120 °C, with stirring at 120 °C continued for 4 h. [f]Catalyst and ligand used in a 1:1 ratio.

number of terminal alkenes, each possessing a suitably conjugated Michael-type acceptor (Table 3). This domino process allowed access to a series of tetrahydro-β-carboline scaffolds, containing a variety of sites available for further functionalization.

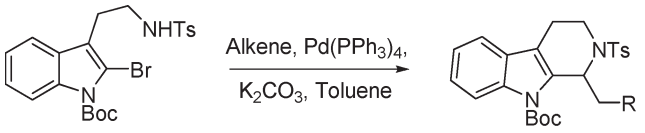
The two-step domino process performed well for all alkenes employed (except in the case of acrylic acid) with isolated yields ranging from 64 to 83% (Table 3).

In conclusion, a novel domino Heck–aza-Michael reaction has been developed. This methodology has been applied to the synthesis of a series of C1-substituted tetrahydro-β-carbolines. Using mild conditions, this domino process affords indole-based heterocyclic scaffolds, highly amenable to larger total syntheses. Furthermore, the domino Heck–aza-Michael conditions reported by Hanson et al. failed for those systems in which the sulfonyl moiety was not contained *within* the heterocyclic ring formed.[8c] The domino Heck–aza-Michael process reported herein proved successful in the synthesis of tetrahydro-β-carbolines with the sulfonyl group *external* to the newly constructed heterocycle. To the best of our knowledge, this is the first example of a domino Heck–aza-Michael reaction for the synthesis of a carbon–nitrogen heterocycle. Complementing existing methodology, this domino process

(17) Our attention turned to the optimal conditions to bring about a simple 1,4-addition. In this case, the tosylamine tether was reactive enough for aza-Michael addition to occur under mild basic conditions.

(18) The phase transfer agent used in an attempt to improve the solubility of K_2CO_3 failed to significantly increase the yield.

TABLE 3. Preparation of Diverse 1-Substituted THβCs



13a 14a, 15-20

entry	alkene	R	product	yield (%)
1	butyl acrylate	$CO_2(CH_2)_3CH_3$	**14a**	83
2	methyl acrylate	CO_2CH_3	**15**	79
3	2-hydroxyethyl acrylate	$CO_2(CH)_2OH$	**16**	64
4	acrolein	CHO	**17**	64
5	acrylamide	$CONH_2$	**18**	80[a]
6	acrylonitrile	CN	**19**	67
7	acrylic acid	CO_2H	**20**	0

[a]Conversion calculated for desired product; however, partial Boc deprotection during synthesis resulted in an inseparable mixture of indole *N*-Boc and indole *N*-H tetrahydro-β-carbolines. See Supporting Information.

allows synthetic flexibility when access to a specific C1-substituted tetrahydro-β-carboline is required.

Current work within this group is focused on variations of this domino process, including the use of more highly substituted alkenes and the introduction of chirality through the use of tryptophan-derived starting materials.

Experimental Section

Typical Procedure for the Preparation of 1-Substituted THβCs 14a, 15−19 (Butyl Acetate THβC 14a as Example). A sealed tube containing a 2-bromoindole **13a** (100 mg, 0.20 mmol), $Pd(PPh_3)_4$ (23 mg, 10 mol %), K_2CO_3 (84 mg, 0.61 mmol), and butyl acrylate (29 mg, 0.22 mmol) in toluene (4 mL) was heated at 120 °C for 16 h. The reaction mixture was cooled to room temperature, the solvent removed in vacuo, and the crude product purified by column chromatography (1:4 EtOAc/Pet Sp) to afford the tetrahydro-β-carboline **14a** (91 mg, 0.17 mmol, 83%) as a pale yellow oil: FT-IR (ν, cm^{-1}, KBr) 1730vs, 1457, 1374, 1324, 1159, 747; ^1H NMR (400 MHz, $CDCl_3$, δ) 8.10 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.14−7.28 (m, 3H), 7.03 (d, J = 8.6 Hz, 1H), 6.12 (dd, J = 3.6 and 10.6 Hz, 1H), 4.05 (m, 3H), 3.50 (m, 1H), 3.00 (dd, J = 3.7 and 14.3 Hz, 1H), 2.70 (dd, J = 10.6 and 14.3 Hz, 1H), 2.39−2.60 (m, 2H), 2.18 (s, 3H), 1.75 (s, 9H), 1.60 (m, J = 7.8 Hz, 2H), 1.34 (m, J = 7.6 Hz, 1H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 169.8, 149.9, 143.4, 137.5, 135.9, 133.0, 129.2, 128.6, 127.1, 124.8, 122.9, 118.0, 115.7, 114.9, 85.0, 64.9, 51.1, 40.3, 37.9, 30.6, 28.4, 21.4, 19.7, 19.2, 13.8; HRMS-ESI (m/z) $[C_{29}H_{36}N_2O_6S - H]^-$ calcd 539.22213, found 539.22187.

Supporting Information Available: Experimental procedures, characterization, copies of ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.