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Access to 1-indolyltetrahydro-β-carbolines *via* metal-free cross-dehydrogenative coupling: the total synthesis of eudistomin U, isoeudistomin U and 19-bromoisoeudistomin U†

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A highly selective and captivating metal-free cross-dehydrogenative coupling for the cross-coupling of two reactive nucleophiles such as tetrahydro-β-carboline and indoles is developed. A series of 1-indolyltetrahydro-β-carboline derivatives were synthesized in excellent to moderate yields. Temperature, time and concentration control resulted in mono indolylation selectively. Moreover, the total synthesis of eudistomin U and isoeudistomin U and the first total synthesis of 19-bromoisoeudistomin U were accomplished.

Construction of a carbon–carbon bond plays an exemplary role in organic synthesis and serves as the heart of classical and modern synthetic organic chemistry.[1] For many years, transition metal-catalysed traditional cross-couplings were mainly used for C–C bond formation.[2] Conventional metal-catalysed coupling reactions employ pre-functionalized electrophiles and nucleophiles, and result in stoichiometric amounts of waste during the transmetalation step. Besides, the pre-functionalized electrophiles used in traditional coupling reactions are either directly or indirectly obtained from the corresponding C–H nucleophiles.

To minimize the waste production and address environmental issues, scientists started developing much greener and environmentally benign synthetic reactions.[3] If two C–H nucleophiles are coupled directly without any pre-functionalization, then the by-product would be hydrogen, and also the waste production will be minimized. The coupling of two nucleophiles seemed to be highly imaginary until oxidative cross-coupling strategies were developed.[3] The future of organic synthesis relies on such oxidative cross-coupling strategies as they have the potential to make synthetic organic chemistry more economical and much eco-friendlier. C–H bonds can generally be classified as reactive and non-reactive. Combinations of transition-metal catalysts, oxidants, and mostly high temperatures are generally needed to activate non-reactive C–H bonds (C–H activation).

Oxidation of the C–H bond becomes easy when it accompanies a hetero-atom (O, N, and S) at the adjacent position (reactive nucleophiles). In oxidative coupling reactions, one of the two nucleophiles involved in the C–C bond formation is *in situ* converted into an electrophile by means of oxidizing reagents (NCS, NBS, ^{t}BuOCl, DDQ, TEMPO salts, and transition metal catalysts). On the other hand, such reactions are highly prone to side reactions (homocoupling, coupling of oxidizing reagents with one of the reactants, over-oxidation, *etc.*) and poor selectivity. The situation becomes very tough to handle when both the nucleophiles involved in the oxidative cross-coupling are highly reactive. The specific choice of reagents and reaction conditions may solve the issues experienced during the coupling of highly reactive nucleophiles.

Tetrahydro-β-carboline (THβC) (**1**) is an annulated indole that is highly reactive and present in many biologically active alkaloids.[4a–d] Also, many exciting alkaloids are mentioned in the literature with the combination of THβC (**1**) and indole (**2**) (Fig. 1). Developing cross-dehydrogenative coupling (CDC) for the coupling of reactive nucleophiles such as indoles and THβC will address the problems associated with the CDC reaction of reactive nucleophiles and also afford biologically important 1-indolyltetrahydro-β-carboline (**6**) derivatives. Though the oxidation of secondary amine is relatively difficult, the reactivity of indole allows the substrate to undergo further oxidation followed by coupling with one more molecule of indole.[5a]

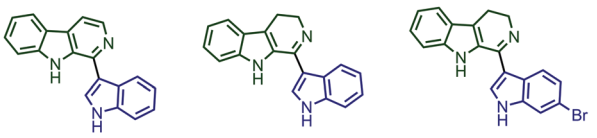

Fig. 1 Examples of 1-indolyl-β-carboline alkaloids.

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Hence, it will be highly difficult to obtain the mono indolyl products selectively. Since THβC is also reactive, there is a possibility of cleavage of the ring under oxidative conditions,[5b] due to which no direct CDC methodologies were explored with the combination of THβC and indole. Preparation of 1-indolyl THβC relies on the Pictet–Spengler reaction or less selective chloroindolenine intermediates (Fig. 2).[5c,d] Hence, we aimed to develop a CDC reaction for the coupling of indole (**2**) and THβC (**1**). In the literature, only two reports were found in which CDC is employed for the coupling of tetrahydro-β-carboline with alkenyl/aryl boronates,[6] and to the best of our knowledge, no reports were found on the direct CDC of the two reactive nucleophiles such as simple THβC (**1**) and indole (**2**) to afford mono indolyltetrahydro-β-carbolines selectively. Keeping the literature gap in mind, we started reaction optimization with different oxidizing reagents and solvents at various temperatures and times (Table 1). *N*-Chlorosuccinimide (NCS) (five minutes of stirring after the addition of NCS and then indole (**2a**) was added, followed by 10 minutes of stirring before quenching the reaction) resulted in only 10% of the cross-coupled product **6a** (Table 1, entry 1). By decreasing the reaction time to 5 minutes (two minutes of stirring after adding NCS and then indole (**2a**) was added, followed by 3 minutes of stirring before quenching the reaction), we could get the aimed coupled product selectively without any over oxidation but the conversion was only about 50% (Table 1, entry 2). When ^{t}BuOCl, NaOCl and DIB were employed as oxidizing agents, no mono indolyl product **6a** formation was observed (Table 1, entries 3–5). With DDQ in DCM (after adding DDQ 1.5 h of stirring and then indole (**2a**) addition, followed by 30 minutes of stirring before quenching the reaction), 40% of the coupled product was formed (Table 1, entry 6). During the course of optimization, we understood that the time required for the oxidization of THβC **1a** is also crucial. We carried out many reactions by increasing the time for the initial oxidation of THβC **1a**, and using DDQ, none of our attempts improved the yield of the reaction. Then we prepared a Bobbitt salt and employed it as an oxidizing reagent, and 25% and 50% of coupled product **6a** were obtained at 0 °C and −20 °C within 150 seconds, respectively (Table 1, entries 7 and 8). Surprisingly, the yield of the coupled product **6a** increased to 82% when the concentration of the reaction decreased to 0.06 M (Table 1, entry 9). When we employed triphenylcarbenium salts as oxidizing agents, fortunately, the yield of the reaction was further improved.

Hexafluorophosphate salt of the trityl cation afforded 85% of **6a**, whereas the tetrafluoroborate salt of the same furnished

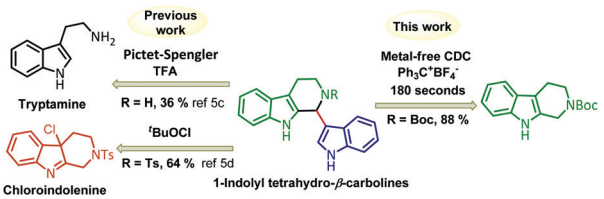
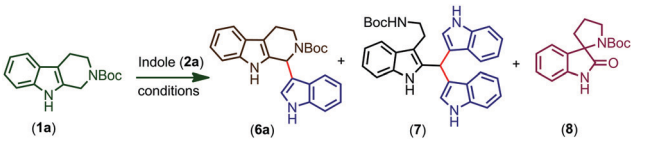


Fig. 2 Previous reports on the synthesis of 1-indolyl THβCs.

Table 1 Optimization of the reaction conditions



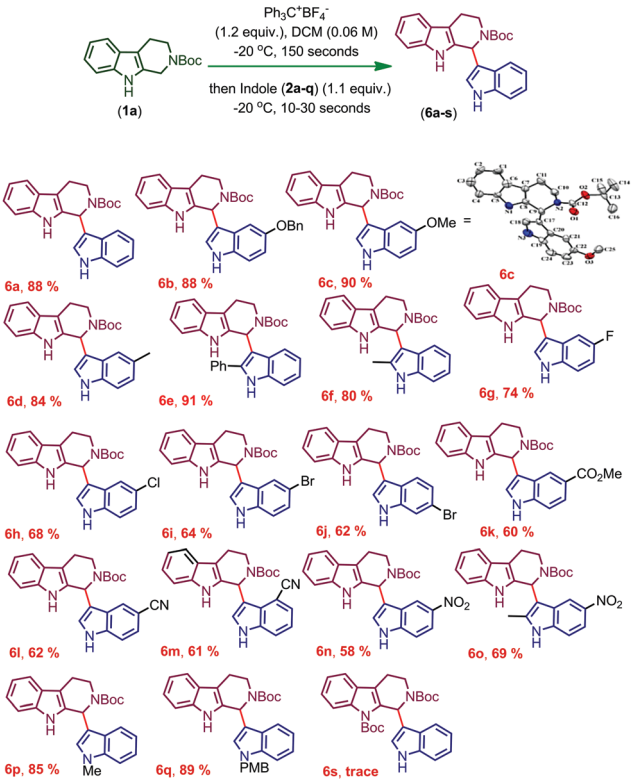
S. no[a]	Oxidizing reagent	Solvent	T (°C)	Time (min)	Yield[f] (%) 6a	7	8
1[b]	NCS (1.0 equiv.)	1,4-Dioxane	r.t.	15.0	10	60	20
2[b]	NCS (1.0 equiv.)	1,4-Dioxane	r.t.	5.0	50	—	—
3[b]	^{t}BuOCl (1.3 equiv.)	EtOAc–H_2O	r.t.	5.0	—	70	20
4[b]	NaOCl (2.0 equiv.)	DCM–H_2O	r.t.	120	—	—	—
5[b]	DIB (1.0 equiv.)	DCM	r.t.	60	—	—	—
6[b]	DDQ (1.0 equiv.)	DCM	r.t.	120	40	—	—
7[bc]	$T^+BF_4^-$	DCM	0	2.5	25	75	—
8[bc]	$T^+BF_4^-$	DCM	−20	2.5	50	50	—
9[cd]	$T^+BF_4^-$	DCM	−20	2.5	82	—	—
10[e]	$Ph_3C^+PF_6^-$	DCM	−20	3.0	85	—	—
11[e]	**$Ph_3C^+BF_4^-$**	**DCM**	**−20**	**3.0**	**88**	**—**	**—**
12[e]	$Ph_3C^+BF_4^-$	DME	−20	3.0	70		
13[e]	$Ph_3C^+BF_4^-$	THF	−20	3.0	72	—	—
14[e]	$Ph_3C^+BF_4^-$	Toluene	−20	3.0	60	—	—
15[e]	$Ph_3C^+BF_4^-$	EtOAc	−20	3.0	58	—	—
16[e]	$Ph_3C^+BF_4^-$	1,4-Dioxane	−20	3.0	24	—	—
17[e]	$Ph_3C^+BF_4^-$	$CHCl_3$	−20	3.0	45	—	—
18[e]	$Ph_3C^+BF_4^-$	DCE	−20	3.0	54	—	—

where T = temperature. [a] Reaction conditions: **1a** (0.18 mmol, 1 equiv.), **2a** (0.2 mmol, 1.1 equiv.), oxidizing reagent (2.2 mmol, 1.2 equiv.) unless otherwise mentioned, solvent (3 mL). T = TEMPO. [b] Reaction concentration is 0.2 M. [c] 2 Minutes of stirring after adding the oxidizing reagent and 30 seconds of stirring after adding indole **2a**. [d] Reaction concentration is 0.06 M. [e] 2.5 Minutes of stirring after adding the oxidizing reagent and 30 seconds of stirring after adding indole **2a**, and the reaction concentration is 0.06 M. [f] Isolated yields.

88% of **6a** in 180 seconds (Table 1, entries 10 and 11). By screening various solvents, we understood that DCM is the best solvent to achieve the targeted compound **6a** as a major compound (Table 1, entries 11–18).

After completing the optimization of the reaction conditions for the synthesis of **6a**, we started the investigation of the substrate scope of trityl salt mediated CDC of Boc protected THβC (**1a**) with different indoles (**2a–q**) possessing electron donating and electron withdrawing substitutions (Scheme 1). Indoles with EDGs reacted extremely faster and afforded good to excellent yields of the products (**6b–f**), and the structure of **6c** was confirmed using X-ray crystallography (CCDC† number: 1973061). Indoles with EDGs at the second position reacted very fast and also resulted in an excellent yield of the products (**6e**, **6f**). Due to the combined effect of electron donating and electron withdrawing nature of halogens, moderate yields of the product were obtained when the halogens were present on indole (**6g–j**). As expected, indoles with strong EWGs further resulted in a decreased conversion and therefore gave only a moderate yield of the coupled products (**6k–n**).

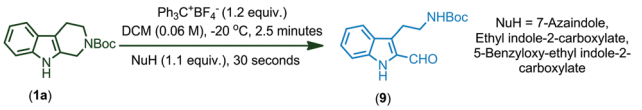
Increasing the time of the reaction (to improve the conversion) resulted in a further decrease in the yield of the product in the case of indoles having EWGs (**6k–n**). Gratifyingly, when an EDG was introduced at the second position of the indole possessing an EWG already on its ring, the conversion and



Scheme 1 Substrate scope (synthesis of derivatives of **6a**).[a,b]: [a]Reaction conditions: tetrahydro-β-carboline **1a–c** (0.185 mmol, 1.0 equiv.), Trityl salt (0.222 mmol, 1.2 equiv.), indoles **2a–q** (0.204 mmol, 1.1 equiv.), and DCM (3.0 mL, 0.06 M), 30 seconds. For substrates **2e** and **2f**, the reaction time is 10 seconds after the addition of indole. [b]Isolated yields.

yield of the reaction were further improved (**6o**). Moreover, the protection of indole N–H with electron releasing groups also resulted in a good yield of the coupled products (**6p**, **q**). In the case of *N*-benzyl protected THβC (**1b**), no coupled product was observed and when both the N–H groups of tetrahydro-β-carboline were protected with Boc groups (**1c**), trace amounts of coupled product **6s** were obtained (confirmed by TLC). As the nucleophilicity is not sufficient enough to undergo the CDC reaction, no coupled product was observed when 7-azaindole, 3-methylindole, ethyl indole-2-carboxylate, and 5-benzyloxy-ethyl indole-2-carboxylate were used and only oxidative cleavage of tetrahydro-β-carboline (**1a**) was observed in such cases to afford compound **9** (Scheme 2). Also, a gram scale synthesis of **6a** was performed, which resulted in 82% yield (see the ESI†).

In addition, rotamers were found in most of the cases and can be differentiated only in the aliphatic region of the THβC and Boc group of the coupled products. To prove the rotamer formation, we have conducted high temperature NMR by taking **6c** as a model substrate, and delightedly, at a higher temperature, multiple peaks that formed at room temperature were merged. Besides, indoles with bulky groups at the 2- and 4-positions did not show rotamer formation (**6e**, **6f**, **6m** and **6o**). After deprotecting the Boc group of **6a**, the rotamers disappeared (**10**, see the ESI†), which confirms that the rotamers are formed due to the presence of the Boc group.



Scheme 2 Oxidative cleavage of tetrahydro-β-carboline.[a,b] [a]Reaction conditions: tetrahydro-β-carboline **1a** (0.185 mmol, 1.0 equiv.), Trityl salt (0.222 mmol, 1.2 equiv.), NuH (0.204 mmol, 1.1 equiv.), and DCM (3.0 mL, 0.06 M), [b]Isolated yields.

The proposed mechanism for the trityl salt mediated CDC of tetrahydro-β-carboline **1a** with indole **2a** and oxidative ring opening by water is described in Fig. 2. The trityl cation oxidizes the compound **1a** and affords the intermediate (i) which on nucleophilic attack of indole furnishes the product **6a.** When the nucleophilicity of indole is not sufficient enough to couple, attack of water followed by *in situ* acidic ring opening results in oxidative cleavage of **6a** to afford compound **9** (Fig. 3).

After analysing the substrate scope of the reaction, we attempted the total synthesis of alkaloid eudistomin U (**3**) (Scheme 3). Eudistomin U (**3**) is a 1-indolyl-β-carboline alkaloid (Fig. 1) and exhibits a wide spectrum of biological properties.[7] Eudistomin U (**3**) and isoeudistomin U (**4**) were isolated from the marine ascidian *Lissoclinum fragile* by Francisco *et al.* in the year 1994.[7a] 19-Bromoisoeudistomin U (**5**) was isolated from the marine ascidian *Eudistoma* along with isoeudistomin U (**4**) in the year 1996.[7b] Structural revision of isoeudistomin U (**4**) was reported by its synthesis in the year 1995,[7c] whereas the synthesis of alkaloid **5** is not known to date. In 1995, Molina and co-workers successfully completed the first total synthesis of eudistomin U (**3**).[8a] Later, a couple of reports were found on the synthesis of **3**.[5d,8b–m] We would like to apply the trityl salt mediated CDC reaction followed by an oxidation/aromatization strategy for the total synthesis of **3**, **4** and **5**. Compound **6a** on Boc deprotection using HCl in 1,4-dioxane afforded compound **10**, which on further aromatization using 10% Pd/C in xylene at 140 °C for 6 hours furnished the target alkaloid eudistomin U (**3**) in 66% yield (over 2 steps). Compound **10** on partial aromatization with IBX afforded the isoeudistomin U in 56% yield (over 2 steps) and compound **6j**, on deprotection followed by partial oxidation with IBX, furnished 19-bromoisoeudistomin U in 60% yield (over 2 steps) (Scheme 3, see the ESI,† Table S1).

To conclude, a highly selective and rapid metal-free cross-dehydrogenative coupling strategy for the coupling of highly

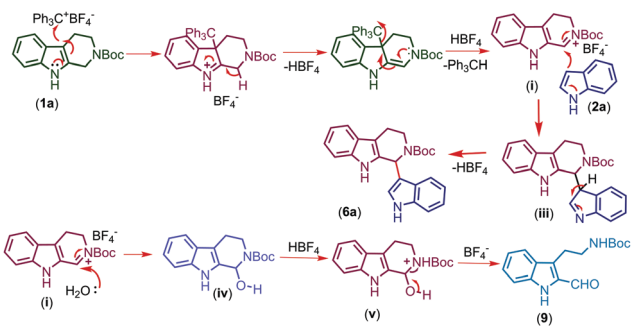
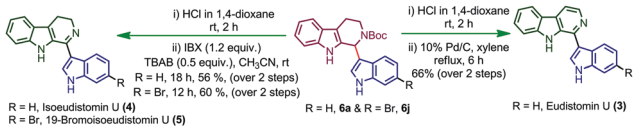


Fig. 3 Proposed mechanism of reaction.



Scheme 3 Total synthesis of eudistomin U (**3**), isoeudistomin U and 19-bromoisoeudistomin U (**5**).

reactive nucleophiles such as tetrahydro-β-carboline and indoles was demonstrated successfully. Insights into the factors governing the reactivity and reaction's selectivity opened the door to solving the puzzles in the chemistry of highly reactive nucleophiles under CDC conditions. By tuning the solvent concentration, temperature, time and addition mode, we could achieve biologically important mono indolyltetrahydro-β-carboline derivatives **6a–s** selectively in excellent to moderate yields. In addition, the total synthesis of alkaloids, eudistomin U (**3**), and isoeudistomin U (**4**) and the first total synthesis of 19-bromoisoeudistomin U (**5**) were successfully completed with overall yields of 58%, 56%, 37%, respectively, in just 3 steps.

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Conflicts of interest

There are no conflicts to declare.

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