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Enantioselective C2-alkylation of indoles via a redox-relay Heck reaction of 2-indole triflates

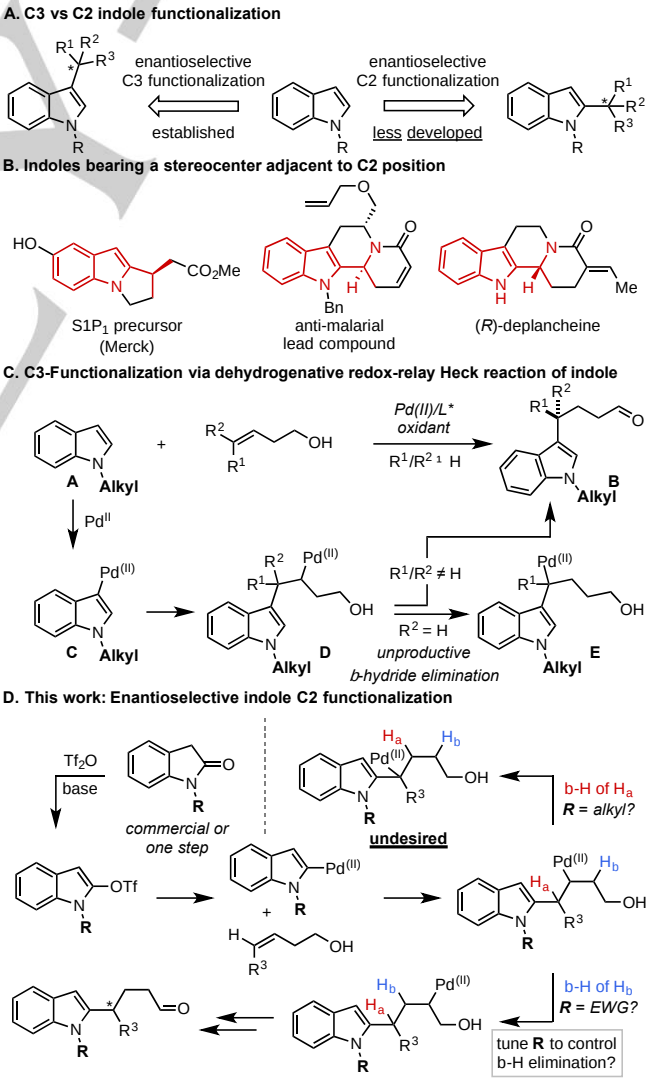
Nicholas J. Race,[#] Qianjia Yuan,[#] and Matthew S. Sigman*[a]

Abstract: A palladium-catalyzed enantioselective redox-relay Heck reaction of 2-indole triflates and disubstituted alkenes is reported. This process combines readily-available indole triflates with a variety of alkenes to afford a range of indole derivatives bearing a stereocenter adjacent to C2. Enantioselectivity is achieved through use of a simple pyridine-oxazoline ligand. Tuning the electronics of the indole, through judicious choice of *N*-protecting group, is required to ensure selective β-hydride elimination away from the indole core. Utility of this method is highlighted in a modular formal synthesis of an $S1P_1$ agonist precursor developed by Merck.

Indole is a privileged scaffold in a wide variety of research areas, including natural product synthesis, pharmaceuticals, agrochemicals and material science.[1] As a result, numerous synthetic methods have been developed for the synthesis and functionalization of indole. Catalytic, *enantioselective* functionalization of the indole core represents an intensive area of research, with most methods exploiting the inherent nucleophilicity at the C3 position for enantioselective Friedel-Crafts-like chemistry (Scheme 1A).[2] For example, we recently reported a palladium-catalyzed dehydrogenative relay-Heck arylation of indole derivative **A** and trisubstituted alkenols to afford aldehydes of type **B** (Scheme 1C).[3] Given that palladation of indole is proposed to occur in a Friedel-Crafts-like manner (**A** → **C**, Scheme 1C),[4] functionalization of the C3 position is observed exclusively.

In contrast, methods to enantioselectively functionalize the indole C2 position are much less developed.[5] In fact, incorporation of a substituent at indole C3 is typically required to promote electrophilic substitution at C2. Therefore, prefunctionalization of the indole is a strategy used to ensure a site-selective reaction. As an example, Macmillan reported a singular case of a conjugate addition reaction of C2-bearing indole potassium trifluoroborate salts to enals using secondary amine catalysis.[6] Given that many natural products and pharmaceutical relevant core structures contain a stereocenter adjacent to the C2 position (Scheme 1B),[7-9] we considered strategies to apply a redox-relay Heck type reaction[10] using an appropriately functionalized indole starting material for the purposes of enantioselective indole C2 functionalization. By coupling this starting material with a diverse selection of alkene coupling partners, we would be able to streamline access to a wide variety of enantioenriched molecular scaffolds.

Two design elements were considered to accomplish such a reaction: 1) as indole derived triflates are readily accessible from simple oxindole starting materials and the corresponding alkenyl triflates have been demonstrated as excellent coupling partners in related Heck reactions,[10d-f] these electrophiles were selected for investigation and 2) the nature of the indole nitrogen substituent was deemed important with an electron withdrawing group possibly required to dissuade the Pd from migrating towards the indole (Scheme 1D).[10d] This was hypothesized on the basis of previous mechanistic work wherein the Pd-catalyst has the propensity to migrate toward more electron rich features of the alkyl chain. Indeed, use of disubstituted alkenols in the dehydrogenative arylation with indole did not lead to the desired relay product as a consequence of the electron-rich indole nucleus (Scheme 1C). Specifically, intermediate **D** underwent selective β-hydride elimination of R^2 (R^2 = H) and subsequent reinsertion of the Pd(II)-hydride afforded Pd(II)-alkyl **E,** which decomposed via expulsion of Pd(0) as promoted by the electrons on the indole nitrogen.



Scheme 1 Catalytic site-selective functionalization of the indole nucleus

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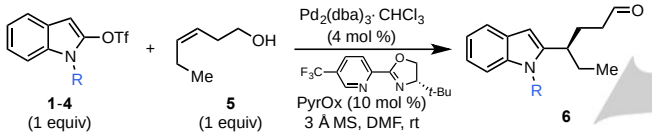
On the basis of the design principles described above, a series of four indole triflates (**1**-**4a**) were synthesized with different substituents on the indole nitrogen. These substrates were evaluated with *cis*-3-hexen-1-ol (**5**) under previously reported conditions reported for alkenyl triflates, which use a Pd(0) precatalyst and a chiral pyridine-oxazoline ligand (Table 1).[10d,11] No desired reaction was observed with either methyl-, phenyl- or acetyl-substituted indole triflate **1**-**3** due to decomposition of the starting materials under the reaction conditions (Entries 1–3). The desired reaction was observed with ethyl carbamate-protected indole triflate **4** wherein aldehyde **6** was isolated in 19% yield and 95:5 er (Entry 4). Addition of two equivalents of alkenol **5** increased the yield to 28% (Entry 5). Given that the Heck reaction generates an equivalent of TfOH every catalyst turnover, we hypothesized that buildup of acid could be problematic, including decomposition of the starting material through carbamate deprotection. To improve the yield, a variety of basic additives were examined in the reaction including K_2CO_3, 3,5-*di*-*tert*-butyl-4-methypyridine, and $Ca(OH)_2$ (Entries 6-8).[10f] Addition of one equivalent of $Ca(OH)_2$ improved the yield of aldehyde **6** to 47%, with no loss in enantioselectivity. The yield of **6** was improved further to 55% by increasing the catalyst loading to 5 mol % (Entry 9).

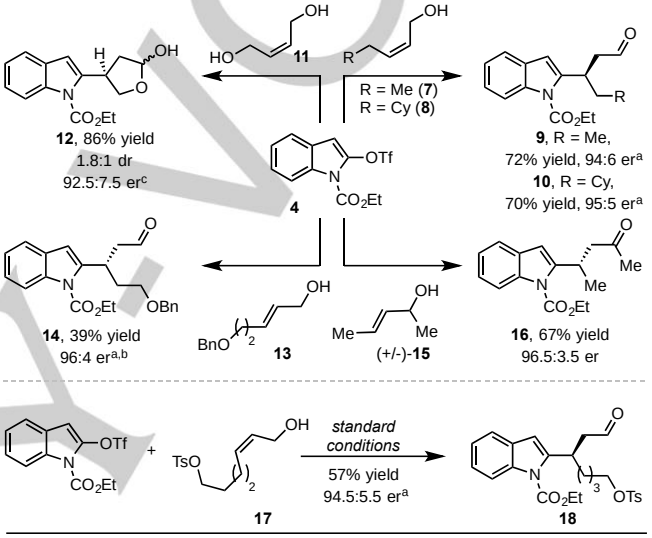


Entry	R	Additive	Result[a]
1	Me (**1**)	-	decomp.
2	Ph (**2**)	-	no product
3	Ac (**3**)	-	decomp.
4	CO_2Et (**4**)	-	19% Yield, 95:5 er
5[b]	CO_2Et (**4**)	-	28% Yield, 95:5 er
6[b]	CO_2Et (**4**)	K_2CO_3 (1 equiv.)	19% Yield, 95:5 er
7[b]	CO_2Et (**4**)	DTBMP (1 equiv.)	28% Yield, 95:5 er
8[b]	CO_2Et (**4**)	$Ca(OH)_2$ (1 equiv.)	47% Yield, 95:5 er
9[b,c]	CO_2Et (**4**)	$Ca(OH)_2$ (1 equiv.)	55% Yield, 95:5 er

[a] Isolated yield, er determined after $NaBH_4$ reduction to alcohol [b] Two equivalents of **5** [c] [Pd] (5 mol %), PyrOx (12 mol %)

Table 1. Reaction optimization

As the next step, we set out to demonstrate the reaction's utility for accessing a wide range of molecular architectures bearing a secondary stereogenic center α to an indole C2 position. Use of simple allylic alcohols **7** and **8** afforded the corresponding aldehydes **9** and **10** in 72% (94:6 er) and 70% yield (95:5 er), respectively (Scheme 2). As highlighted in the introduction, access to aldehydes bearing a β-substituted C2-indole is possible via iminium ion catalysis.[6] We therefore chose to focus our attention on alkene substrates that provide products not accessible using these methods. For example, coupling of **4** and diol **11**[12] afforded lactol **12** in 86% yield, 1.8:1 dr. The enantiomeric excess for this product (92.5:7.5 er) was measured after oxidation of the crude lactol to the lactone (see Supporting Information). To the best of our knowledge, enantioselective conjugate additions to lactones at the indole C2 position is unknown. Use of benzylether-substituted allylic alcohol **13** afforded the desired product **14** in modest yield but excellent enantioselectivity. Racemic secondary allylic alcohol **15** afforded the corresponding ketone **16** in good yield and enantioselectivity. The yield of ketone **16** in this reaction is >50%, which suggests the stereocenter formed in the product is under catalyst control and this reaction is not a kinetic resolution. Finally, we explored the use of an allylic alcohol bearing a primary tosyl-protected alcohol (**17**). Under our reaction conditions, the (formal) alkylation occurs selectively between the indole C2 and the alkene carbon distal to the primary unprotected alcohol to give **18** in good yield and enantioselectivity. The resulting tosylate and aldehyde provide useful functional groups for further product manipulation.



[a] Isolated yield, er determined after $NaBH_4$ reduction to alcohol [b] Yield of alcohol, $Pd_2dba_3 \cdot CHCl_3$ (10 mol%), PyrOx (24 mol%) [c] er determined afer CrO_3 oxidation

Scheme 2. Scope of allylic alcohols

Next, we examined the functional group tolerance of the reaction with respect to substituents on the indole ring using homoallylic alcohol **5** (Scheme 3A).[13] Functional groups compatible with this chemistry include chloride (**6b**), esters (**6c**), alkyl ethers and silyl ethers (**6d** and **6f**), boronic esters (**6e**), and bromide (**6g**). It is worth noting that the palladium catalyst initiates selectively at the indole triflate in the presence of the aryl bromide.

The ability to access enantioenriched secondary alkyl stereocenters adjacent to the indole C2 position remotely to the aldehyde functional group is highlighted in Scheme 3B. Primary and secondary bis-homoallylic alkenols **19** and **21** afforded the corresponding relay-Heck products **20** and **22** in moderate yield and enantioselectivity. Accessing these types of enantioenriched products using conventional approaches, for example, using alkylation chemistry, would be extremely challenging.

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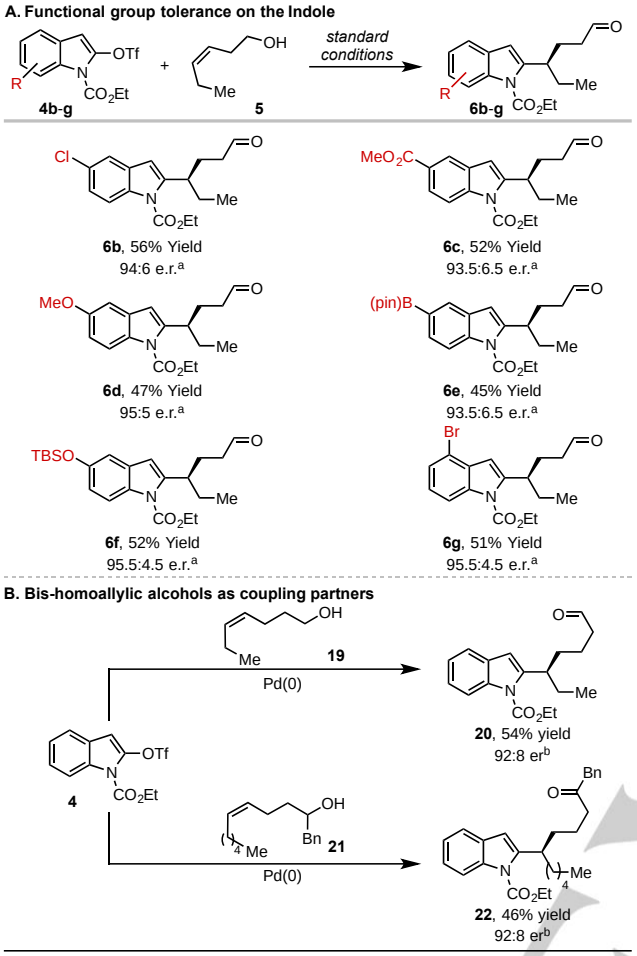
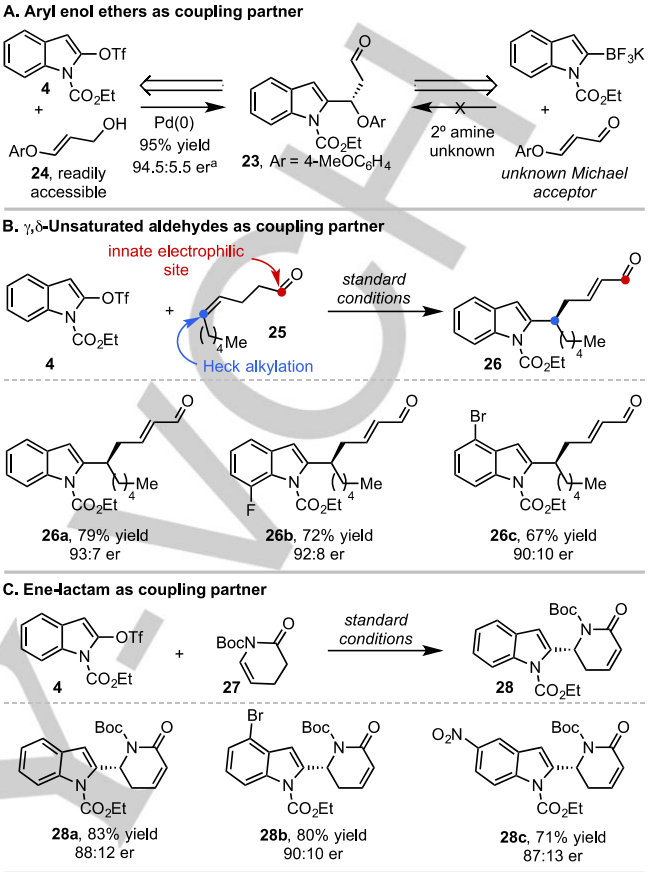


[a] Isolated yield, er determined after $NaBH_4$ reduction to alcohol [b] $Pd_2dba_3 \cdot CHCl_3$ (7.5 mol%), PyrOx (20 mol%), triflate (1 equiv, added in two batches), alkenol (3 equiv)

Scheme 3. Indole scope with homoallylic and bis-homoallylic alkenols.



[a] Isolated yield, er determined after $NaBH_4$ reduction to alcohol

Scheme 4. Indole scope with homoallylic and bis-homoallylic alkenols.

More recently our group has explored alkenes bearing various unique functional groups (Scheme 4). As an example, coupling of indole triflate **4** and enol ether **24** provided aldehyde **23**.[14] This reaction affords an enantioenriched secondary ether adjacent to the indole C2 position, a product not accessible using reported organocatalytic approaches. Use of commercially-available *cis*-4-nonenal **25** afforded α,β-unsaturated aldehydes **26a-c** in high yield and good enantioselectivity.[15] These products are attractive because it is well-established that enantioselective intramolecular cyclizations of related molecules can be promoted by secondary amines.[16] It is also possible to use ene-lactam **27** as a coupling partner in this chemistry, leading to products **28a-c** in excellent yield and slightly diminished enantioselectivity.[17] This reaction provides rapid and modular access to the core of natural products and drug candidates (*vide supra*).

Finally, we wanted to highlight how this indole C2 alkylation process provides highly modular enantioselective formal access to tricyclic indole **31,** which is a key precursor to an $S1P_1$ agonist reported by Merck (Scheme 5).[9] Initially, Merck developed a route involving the *de novo* construction of the indole framework providing efficient access to the indole core. However, it relies on the use of traditional chiral auxiliary chemistry to set the absolute stereochemistry. The relay-Heck reaction conveniently combines two simple building blocks and sets the stereochemistry during C–C bond construction providing a modular strategy to such scaffolds. In the event, indole triflate **4f** and alkene **13** are coupled in moderate yield but excellent enantioselectivity. Processing of the aldehyde through three steps (oxidation, esterification, deprotection) afforded indole **30** in 24% yield from triflate **4f** (96:4 er). This molecule can be further manipulated to produce $S1P_1$ agonist precursor **31** as established by Merck.[9] Optical rotation comparison of **30** to the literature allowed us to confirm the absolute stereochemistry of our product to be (*S*). This stereochemical outcome is consistent with our previously reported model for enantioselective induction in relay-Heck reactions.[9] All other compounds were assigned by analogy to **30**, considering that switching the alkene geometry results in the opposite enantiomer of product being formed.

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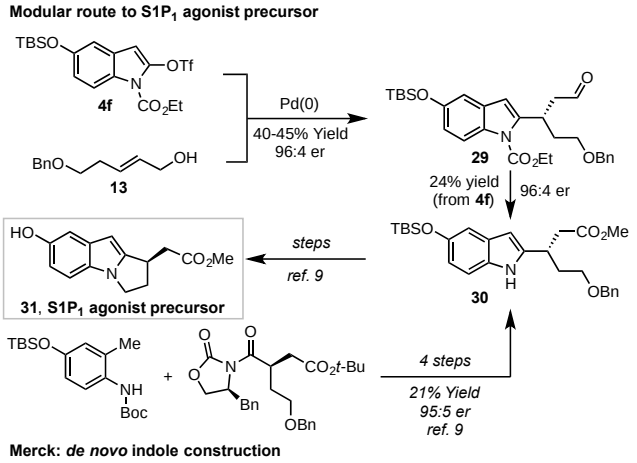

Scheme 5. Formal synthesis of an $S1P_1$ agonist

In conclusion, we have reported an enantioselective C2-alkylation of indole via a redox-relay Heck reaction of indole triflate and alkenes. This reaction provides access to a wide selection of alkylated indole derivatives bearing a stereocenter adjacent to the C2 position and is tolerant of a range of functional groups. We highlighted this method by demonstrating its utility for providing modular formal access to a key tricyclic indole core of a $S1P_1$ agonist precursor. This methodology offers a new disconnection for synthetic chemists and enables the modular exploration of new chemical space in the search for new lead drug compounds.

Acknowledgements

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Keywords: indole • relay-Heck reaction • enantioselective catalysis • palladium

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