Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Rh-catalyzed oxidative C-C bond formation and C-N bond cleavage: direct access to C2-olefinated free (NH)-indoles and pyrroles

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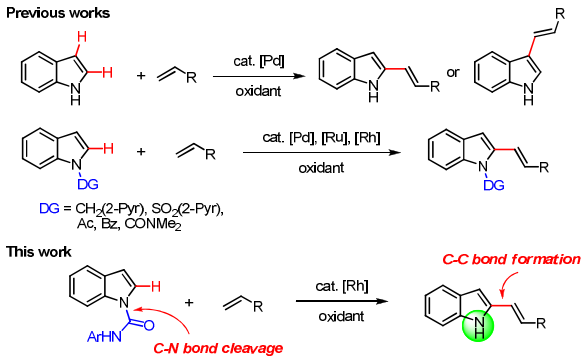
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

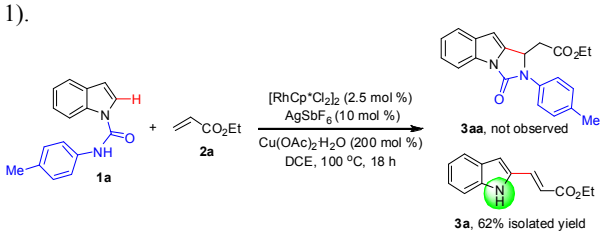
The rhodium-catalyzed oxidative C2-olefination of indoles and pyrroles containing *N*-arylcarboxamide directing groups with a range of alkenes and subsequent cleavage of directing groups is described. This method provides the direct and efficient access to C2-functionalized free (NH)-heterocycles.

The indole nucleus is a ubiquitous structural motif found in bioactive natural products, pharmaceuticals, functional materials, and agrochemicals.[1] Thus the efficient synthesis and functionalization of indoles have been of considerable interest in organic and medicinal chemistry.[2] In particular, transition-metal-catalyzed cross-coupling of indoles and aryl halides is one of the most sustainable protocols for the functionalization of indoles.[3] Since the pioneering efforts of Fujiwara and Moritani,[4] remarkable progress has been focused on the oxidative Heck coupling between indoles and olefins under palladium catalysis via a twofold C–H bond cleavage.[5] Due to the electrophilic nature of the organometallic species involved in the coupling reaction, the reaction to occurs preferentially at the more electron-rich C3 position of the indole ring. Therefore, the highly selective C2-olefination of 2,3-unsubstituted indoles has been an intensive research area to override the inherent selectivity of indoles. For instance, Gaunt described the regioselective Pd-catalyzed intermolecular C2- or C3- alkenylation of free (NH)-indoles by employing different solvents and additives.[5f] Satoh and Miura disclosed the Pd(II)-catalyzed C–H alkenylation and subsequent decarboxylation protocol of indole-3-carboxylic acids to afford exclusively C2-alkenylated indoles, where the carboxyl group blocks the C3-position and acts as a removable directing group.[5j] Recently, Carretero reported the highly efficient Pd-catalyzed C2-selective olefinations of indoles and pyrroles assisted by a removable *N*-(2-pyridyl)sulfonyl group.[5k,l] In contrast to the vast majority of documents on the palladium-catalyzed olefinations, the indolic C–H olefinations using rhodium or ruthenium catalysts, which often allow higher selectivities and broad substrate scope, have been much less explored. For example, Glorius first reported a single example for Rh-catalyzed C2-olefination of *N*-acetyl indoles.[6] Prabhu demonstrated Ru-catalyzed oxidative C2-alkenylation of indoles using the *N*-benzoyl directing group.[7] Recently, Li and Wang[8] and Song,[9] respectively, reported Rh(III)- and Ru(II)-catalyzed oxidative couplings between indoles containing a *N*,*N*-dimethylcarbamoyl group and olefins to afford C2-alkenylated indoles (Scheme 1).



Scheme 1 Transition-metal-catalyzed oxidative C2-olefination protocols of indoles with alkenes.

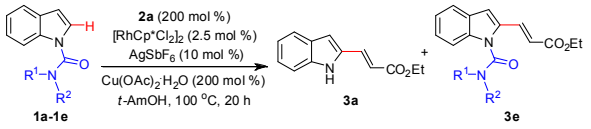
Our initial investigation focused on the construction of a unique tricyclic framework, imidazo[1,5-a]indol-3-one **3aa**, through a tandem C2-alkenylation and intramolecular cyclization between indole **1a** containing an *N*-arylcarboxamide group with acrylate **2a**.[10] Interestingly, the coupling reaction of **1a** and **2a** in the presence of the cationic rhodium complex, derived from $[Cp^*RhCl_2]_2$ and $AgSbF_6$, and $Cu(OAc)_2$ oxidant in DCE solvent at 100 °C provided the unexpected product **3a** in 62% yield (eq. 1).



(1)

Encouraged by this unprecedented result, we herein report the rhodium-catalyzed C2-selective olefination of *N*-arylcarbamoyl indoles and subsequent cleavage of directing groups. After extensive screening for the optimal reaction conditions, the best results were obtained by the use of 2 equiv. of **2a**, 2.5 mol % of $[RhCp^*Cl_2]_2$ and 2 equiv. of $Cu(OAc)_2 \cdot H_2O$ in *tert*-amyl alcohol (*t*-AmOH) solvent at 100 °C for 20 h, affording our desired product **3a** in 78% yield (Table 1, entry 1) (see Supplementary Information for the detailed optimization table). Next, we examined the influence of carbamoyl directing groups, as shown in Table 1. Free (NH)-indole did not yield any coupling compound under the present reaction conditions (data not shown).

Table 1 Screening of directing groups

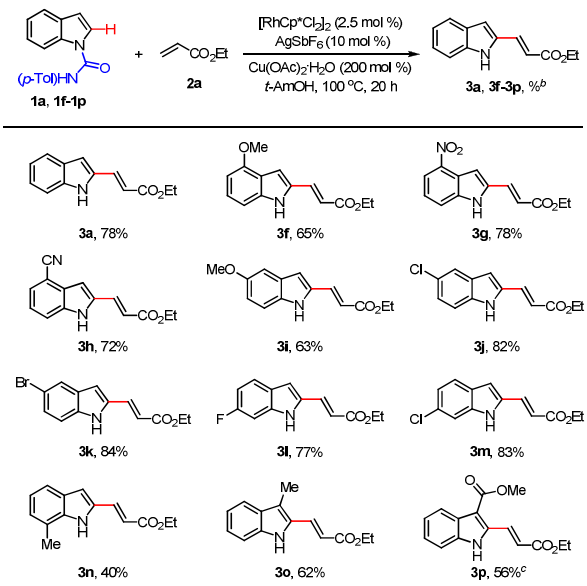


entry	R^1	R^2	substrate	product	yield (%)[a]
1	H	4-MeC_6H_4	**1a**	**3a**	78
2	H	C_6H_5	**1b**	**3a**	65
3	H	4-$MeOC_6H_4$	**1c**	**3a**	72
4	H	*n*-Bu	**1d**	**3a**	42
5	Me	Me	**1e**	**3e**	90

[a] Isolated yields by column chromatography.

Compounds **1b**–**1d**, derived from indole and corresponding isocyanates,[11] were compatible with the optimal reaction conditions to afford our desired product **3a** (Table 1, entries 2–4), whereas *N*,*N*-disubstituted indole **1e** furnished the C2-alkenylated compound **3e** without further removal of a *N*-protection group (Table 1, entry 5).

Table 2 Scope of indoles[a]

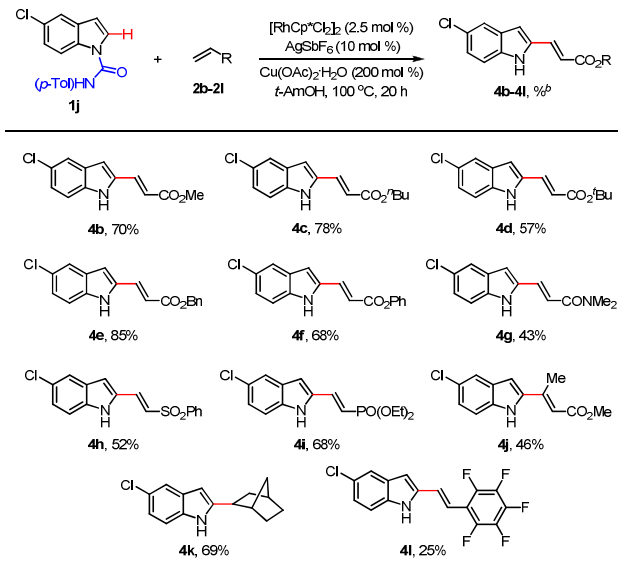


[a] Reaction conditions: **1a** and **1f**–**1p** (0.3 mmol), **2a** (0.6 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (200 mol %), *t*-AmOH (1 mL), 100 °C for 20 h in sealed tubes. [b] Yield isolated by column chromatography. [c] **2a** (0.9 mmol), 36 h.

With the optimized reaction conditions in hand, the scope and limitation of indoles **1f**–**1p** with *N*-(*p*-tolyl)carboxamide directing group were investigated, as shown in Table 2. The coupling of ethyl acrylate (**2a**) and indoles **1f**–**1n** with electron-rich and electron-deficient groups (OMe, Me, NO_2, CN, F, Cl, and Br), regardless of the substituent position on the phenyl ring, was found to be favored in this reaction to afford the corresponding products **3f**–**3n** in moderate to good yields. Particularly noteworthy was the tolerance of the reaction conditions to bromo and chloro moieties, which provide a versatile synthetic handle for further elaboration of the products. This protocol was also successfully applied for C3-substituted indoles, furnishing the corresponding products **3o** and **3p**.

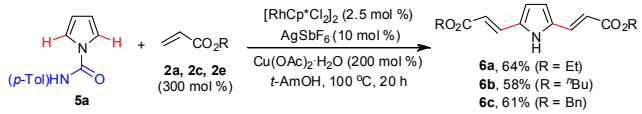
To further explore the substrate scope and limitations, a range of olefins **2b**–**2l** was screened to couple with indole **1j** under optimal reaction conditions (Table 3). To our pleasure, olefins **2b**–**2i** with electron-withdrawing groups proved to be good substrates for this transformation, affording the corresponding products **4b**–**4i**. This reaction was also compatible with 1,2-disubstituted alkenes, such as (*E*)-methyl crotonate **2j**, affording the desired products **4j** with complete (*E*)-stereoselectivity.[12] Interestingly, the coupling of norbornene **2k** with indole **1j** yielded the alkylated product **4k** in 69% yield instead of the expected olefinated one. In contrast, styrene **2l** displayed a relatively decreased reactivity under the present reaction conditions.

Table 3 Scope of olefins[a]



[a] Reaction conditions: **1j** (0.3 mmol), **2b**–**2l** (0.6 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (200 mol %), *t*-AmOH (1 mL), 100 °C for 20 h in sealed tubes. [b] Yield isolated by column chromatography.

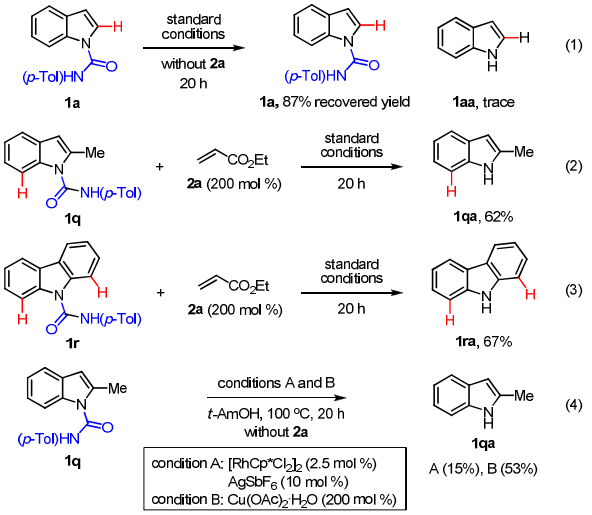
After successful investigation of the oxidative olefination with indoles, we next tried to expand our method to pyrrole, which is a useful building block and the core motif of various natural products and medicinally relevant molecules.[13] To our delight, the coupling reactions between **5a** with *N*-(*p*-tolyl)carboxamide group and acrylates **2a**, **2c** and **2e** were found to be favored in the olefination and subsequent cleavage of directing group to afford the 2,5-bis-olefinated pyrroles **6a**–**6c** in good yields (Scheme 2).



Scheme 2 Expansion of substrate scope to pyrroles.

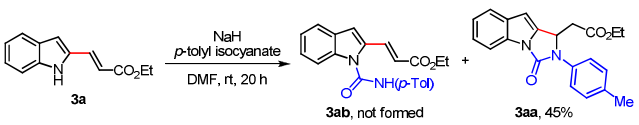
To gain a mechanistic insight of in-situ removal of a directing group, the following experiments were conducted (Scheme 3). First, the treatment of indole **1a** in the absence of acrylate **2a** under the standard reaction conditions provided the starting material **1a** in 87% recovered yield, and a trace amount of **1aa** was observed (Scheme 3, eq. 1). Interestingly, the reaction of C2-

substituted indole **1q** and carbazole **1r** with olefin **2a**, respectively, provided free (NH)-indole **1qa** and free (NH)-carbazole **1ra** instead of C7- or C1-olefinated compounds (Scheme 3, eqs. 2 and 3).[14] These results indicated that the C2-substituents on indoles with a *N*-(*p*-tolyl)carboxamide group might be crucial to facilitate the C–N bond cleavage under the standard reaction conditions. To further probe the role of rhodium catalyst and copper salt, some control experiments were performed (Scheme 3, eq. 4, conditions A and B). A small amount (15%) of **1qa** was obtained without using copper acetate (condition A), while a 53% yield of **1qa** were isolated in the absence of cationic Rh catalyst (condition B), which could be rationalized by assuming that $Cu(OAc)_2$ might play a key role for the deprotection of *N*-arylcarboxamide group.



Scheme 3 Mechanistic investigation.

Gratifyingly, while performing control experiments to prepare compound **3ab**, which can be derived from **3a** and *p*-tolyl isocyanate, our initial target compound imidazo[1,5-a]indol-3-one **3aa** was isolated in 45% yield via tandem *N*-amidation followed by intramolecular cyclization (Scheme 4). This result potentially provides new opportunities to use our method for the construction of bioactive tricyclic indolic derivatives.



Scheme 4 Formation of tricyclic indolic compound.

In conclusion, we developed a novel strategy for the formation of C2-functionalized free (NH)-indoles and free (NH)-pyrroles via the rhodium(III)-catalyzed oxidative alkenylation of *N*-arylcarbamoyl indoles and pyrroles with olefins and subsequent cleavage of a protection group. Further applications to the synthesis of biologically active compounds and a more detailed mechanistic investigation are in progress.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (No. 2013R1A2A2A01005249).

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and spectroscopic data for all compounds. See DOI: 10.1039/b000000x/

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14 Under rhodium and ruthenium catalysis, C2-substituted *N*,*N*-dimethylcarbamoyl indoles or carbazoles provided C7-functionalized indoles or C1-functionalized carbazoles by the formation of 6-membered metallacycles, see: refs. 8 and 9.