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Rhodium(III)-Catalyzed Regioselective Direct C-2 Alkenylation of Indoles Assisted by the Removable N-(2-Pyrimidyl) Group

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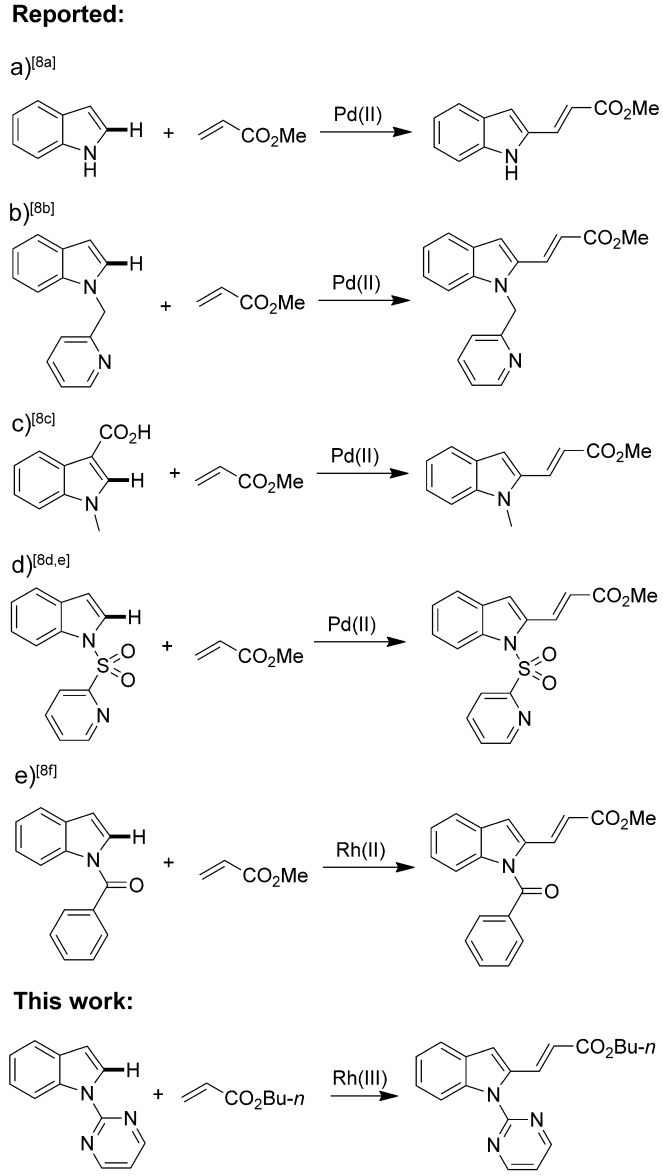
Abstract: The C-2-alkenylindole unit is a key component of numerous natural products and pharmacophores. However, the intermolecular direct construction of the core structural motif remains challenging in organic synthesis. Here we report a new, efficient, and versatile methodology for the synthesis of C-2-alkenylindoles through rhodium(III)-catalyzed direct C–H functionalization of indoles with acrylates under air by employing a metal-directing group strategy. This strategy gives a rare selectivity for the alkenylation N-(2-pyrimidyl)indoles at the C-2 position and provides the functionalized C-2-alkenylindoles under mild conditions with broad substrate tolerance. An expansion of the methodology has also been demonstrated to, for example, the direct alkenylation of pyrrole and facile deprotection of the pyrimidyl group. All the results suggest that this methodology could be served as a highly attractive alternative for the direct construction of biologically important C-2-alkenylindoles.

Keywords: acrylates; C-2 alkenylation; indoles; *N*-(2-pyrimidyl) group; rhodium(III) catalysts

Since indole structures are widely found in numerous natural products, pharmacophores, and synthetic building blocks,[1] the development of methods for building the indole motif has attracted considerable attention in organic synthesis.[2] As a result, direct approaches toward their construction have become competitive with more traditional protocols based on substrate preactivation. Indeed, methods involving transition metal-catalyzed direct functionalization of the indole nucleus are emerging as attractive alternatives because they allow for the atom-economical synthesis of biologically important indoles *via* C–H activation/cleavage.[3] However, compared with the much more developed C–H arylations of indoles,[4,5] catalysts that allow the direct C–H alkenylation are still limited despite the potential utility of such products.[6,7] A particularly challenging transformation is the intermolecular direct C-2 alkenylation of indole with acrylates due to the electrophilic nature of the C-2 position, for which very few metal-catalyzed protocols that only used Pd(II) or Ru(II) as the catalyst have been reported (Scheme 1).[8]

Despite these important advances, there is room for innovation, both in increasing the efficiency of the reaction and in improving the current limited scope of the substrates. For example, Gaunt and co-workers reported Pd(II)-catalyzed and solvent-controlled C-3 or C-2 alkenylation of free NH indoles. However, decreased yields were found in the C-2 alkenylation.[8a] Ricci and co-workers described an efficient Pd(II)-catalyzed C-2 alkenylation of indoles. However, a non-removable *N*-(2-pyridylmethyl) group was used as the directing group in their catalysis.[8b] Recently Miura and co-workers disclosed a versatile Pd(II)-cat-



Scheme 1. The direct C-2 alkenylation of indoles *via* C–H functionalization.

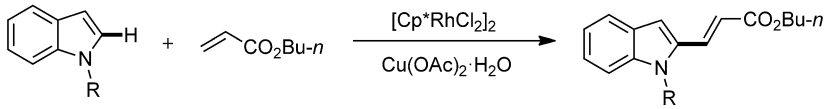
alyzed site-selective C-2 alkenylation of indoles. However, this catalysis needed an additional carboxy group at the C-3 position of indoles for blocking this position.[8c] Therefore it is of utmost importance to develop a new methodology as an alternative to the existing methods for the efficient construction of biologically important C-2-alkenylindoles in synthetic organic chemistry.

On the other hand, so far transition metal-catalyzed C–H functionalization reactions of various aromatic substrates have been successfully developed by employing a directing group-assisted C–H activation strategy.[3,10–12] Among various aromatic substrates and directing groups, indole units bearing the readily installable and removable *N*-(2-pyrimidyl)[5a,7a,11] or N–$(CH_3)_2$–NCO[7c,12] groups for C–H bond activation have attracted particular attention, of which some versatile protocols have stand out. For example, Yoshikai and co-workers developed cobalt-catalyzed C–H functionalization of indoles by using the N-(2-pyrimidyl) as an easily removable directing group.[5a,7a,11a,b] Very recently, Kim and co-workers described an efficient Rh(III)-catalyzed C–H bond activation of indoles with allylic acetates to afford C-2-allylated indoles, where the N–$(CH_3)_2$–NCO was employed as the directing group.[12c] Given these successful examples, we hypothesized that Rh(III) catalysis could be directed toward regioselective C-2 alkenylation of indoles with acrylates using such a directing group strategy.

To test this hypothesis, we first selected well known $[Cp^*RhCl_2]_2$ as the catalyst, used $Cu(OAc)_2{\cdot}H_2O$ as an oxidant, and employed *n*-butyl acrylate and *N*-functionalized indoles bearing various easily attachable groups [N–H, N–Me, N–Boc, N–Ac, N–$(CH_3)_2$–NCO, N–phenylsulfonyl, and N-(2-pyrimidyl)] as the substrates for reaction development, with the aim to find a suitable directing group in the Rh(III) system. As shown in Table 1, the reactions of indoles **1a–g** with **2a** were examined under $[Cp^*RhCl_2]_2$ catalysis (5.0 mol%) with $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.) as an oxidant under air. To our delight, when the N-(2-pyrimidyl) group was employed as the directing group, the reaction occurred at 80 °C in DCE and for 5 h to afford the desired product **3ga** in 69% yield (Table 1, entry 7). Changing DCE to other selected solvents inhibited the process (Table 1, entries 8–12). Among a variety of temperatures, the reaction at 60 °C was found to allow the most efficient catalysis with an improved yield of 85% (Table 1, entries 13–15). No product was obtained in the absence of $[Cp^*RhCl_2]_2$ or $Cu(OAc)_2{\cdot}H_2O$ (Table 1, entries 16 and 17). Changing the oxidant from $Cu(OAc)_2{\cdot}H_2O$ to Ag_2CO_3 or AgOAc gave lower conversion (Table 1, entries 18 and 19). In summary, the optimal conditions in DCE comprise $[Cp^*RhCl_2]_2$ (5.0 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.) at 60 °C for 5 h under air. It is furthermore noteworthy that the inherently reactive C-3 position of indole was untouched in the Rh(III) catalysis.

With the optimized catalytic system in hand, we subsequently explored its scope in the C-2 alkenylation of diverse N-(2-pyrimidyl)indoles (Table 2). In general, the reaction proceeded smoothly to give the desired products in good to excellent yields [48–93%, except **3ha** (25%), the reason for the low yield might be due to the steric effect] and the electronic nature of the substituents on the indole ring did not play a key role. Both electron-rich and electron-poor indoles were good substrates. Substitutions at the C-3 (Table 2, entry 2), C-4 (Table 2, entries 3–5), C-5 (Table 2, entries 6–11), both C-3 and C-5 (Table 2, entries 12 and 13), and C-6 (Table 2, entries 14-17) posi-

Table 1. Selected optimization of reaction conditions.[a]



1a–g 2a 3aa–ga

Entry	R	Indole	Temperature [°C]	Solvent	Product	Yield[b]
1	H	**1a**	80	DCE	**3aa**	0
2	Me	**1b**	80	DCE	**3ba**	0
3	Boc	**1c**	80	DCE	**3ca**	0
4	Ac	**1d**	80	DCE	**3da**	0
5	$(CH_3)_2NCO$	**1e**	80	DCE	**3ea**	0
6	phenylsulfonyl	**1f**	80	DCE	**3fa**	15%
7	2-pyrimidyl	**1g**	80	DCE	**3ga**	69%
8	2-pyrimidyl	**1g**	80	toluene	**3ga**	50%
9	2-pyrimidyl	**1g**	80	dioxane	**3ga**	43%
10	2-pyrimidyl	**1g**	80	ethanol	**3ga**	37%
11	2-pyrimidyl	**1g**	80	DMF	**3ga**	57%
12	2-pyrimidyl	**1g**	80	CH_3CN	**3ga**	45%
13	2-pyrimidyl	**1g**	100	DCE	**3ga**	48%
14	**2-pyrimidyl**	**1g**	**60**	**DCE**	**3ga**	**85%**
15	2-pyrimidyl	**1g**	40	DCE	**3ga**	52%
16[c]	2-pyrimidyl	**1g**	60	DCE	**3ga**	0
17[d]	2-pyrimidyl	**1g**	60	DCE	**3ga**	0
18[e]	2-pyrimidyl	**1g**	60	DCE	**3ga**	8%
19[f]	2-pyrimidyl	**1g**	60	DCE	**3ga**	39%

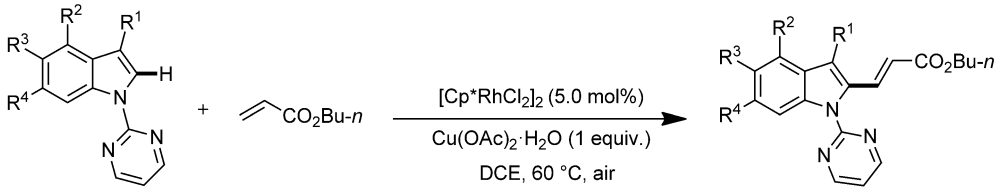
[a] *Reaction conditions:* **1a–g** (0.25 mmol), **2a** (0.30 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (0.25 mmol), in solvent (1.0 mL) under air for 5 h.
[b] Isolated yields.
[c] The reaction was carried out in the absence of $[Cp^*RhCl_2]_2$.
[d] The reaction was carried out in the absence of $Cu(OAc)_2{\cdot}H_2O$.
[e] Using Ag_2CO_3 as the oxidant.
[f] Using AgOAc as the oxidant.

tions were all well tolerated. Furthermore, the reaction showed good compatibility with many valuable functional groups such as methoxy, fluoro, chloro, bromo, iodo, ester, cyano, and nitro substituents (**3ia–ta** and **3va–wa**). Tolerance to the fluoro (**3ma** and **3va**), chloro (**3ka**, **3na** and **3wa**), bromo (**3ra**), iodo (**3sa**), and ester (**3qa–sa**) functional groups is especially noteworthy since they are useful for subsequent cross-coupling reactions.

We also tested several alkyl acrylates with **1g** as a model substrate. As shown in Scheme 2, methyl acrylate (**2b**) coupled efficiently with **1g** to give the corresponding C-2 alkenylation product **3gb** with excellent regioselectivity and in synthetically useful yield (89%). Interestingly, very recently Lanke and Prabhu reported that *N*-benzoylindoles reacted with *tert*-butyl acrylate (**2c**) in their Ru(II) catalysis to furnish the *tert*-butyl-deprotected C-2-acrylic acid indole products in moderate yields (52%–62%).[8f] However, in the developed Rh(III) catalysis, the reaction of **1g** with **2c** offered the desired product **3gc** in a good yield (76%), where the *tert*-butyl part was retained perfectly. This result further illustrates the remarkable robustness of our Rh(III) system.

Encouraged by the above results, we were interested in expanding the versatility of the N-(2-pyrimidyl) group in the alkenylation of other nitrogen heterocycles such as pyrroles, which rival indoles in biological significance and as valuable synthons.[13] Thus, the reaction was investigated using N-(2-pyrimidyl)pyrrole **1y** and *n*-butyl acrylate **2a** as the model substrates with different times at varied temperatures (Table 3). Very interestingly, the reaction for 1 h in the developed Rh(III) catalysis occurred to give the C-2 monoalkenylation product **3ya-a** and the C-2,C-5 dialkenylation product **3ya-b** in 21% and 16% yields, respectively (Table 3, entry 1). Notably, prolonging the reaction time resulted in an enhancement of the yield of **3ya-b** from 16% to 39% accompanied by a decrease in the yield of **3ya-a** from 21% to traces (Table 3, entries 1 *vs.* 2 *vs.* 3). Inspired by the results, we decided to increase the stoichiometry of *n*-butyl acrylate to 3.0 equivalents in the reaction. As expected, the reaction resulted in the regioselective formation of C-2,C-5 dialkenylated **3ya-b** as the sole product in a syntheti-

Table 2. Scope of of the reaction of functionalized indoles with **2a**.[a]



1g–w **2a** **3ga–wa**

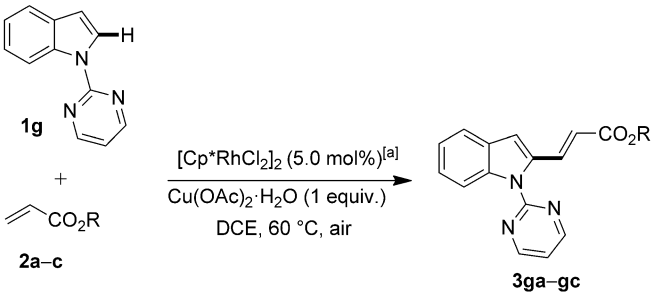
Entry	Indole	R^1 (C-3)	R^2 (C-4)	R^3 (C-5)	R^4 (C-6)	Yield[b]
1	**1g**	H	H	H	H	85%
2[c]	**1h**	CH_3	H	H	H	25%
3	**1i**	H	OCH_3	H	H	79%
4	**1j**	H	CN	H	H	72%
5	**1k**	H	Cl	H	H	51%
6	**1l**	H	H	OCH_3	H	65%
7	**1m**	H	H	F	H	81%
8	**1n**	H	H	Cl	H	67%
9	**1o**	H	H	CN	H	62%
10	**1p**	H	H	NO_2	H	79%
11	**1q**	H	H	COOMe	H	93%
12[d]	**1r**	Br	H	COOMe	H	58%
13[d]	**1s**	I	H	COOMe	H	60%
14	**1t**	H	H	H	OCH_3	78%
15	**1u**	H	H	H	CH_3	48%
16	**1v**	H	H	H	F	75%
17	**1w**	H	H	H	Cl	63%

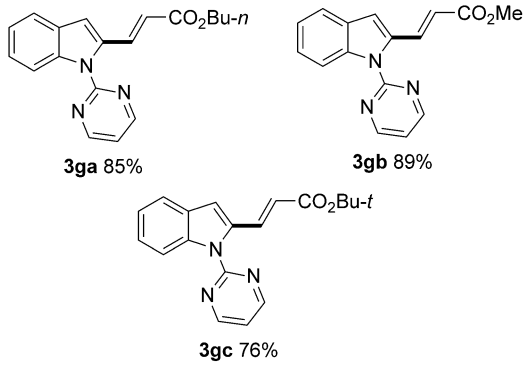
[a] The reaction was carried out using **1g–w** (0.25 mmol), **2** (0.30 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol%), and $Cu(OAc)_2 \cdot H_2O$ (0.25 mmol) under air at 60 °C for 5 h.
[b] Isolated yields.
[c] The reaction time was 12 h.
[d] The reaction time was 72 h.

cally useful yield of 75% (Table 3, entry 4). No reaction was observed at room temperature under otherwise identical conditions (Table 3, entry 5).

Considering the remarkably broad substrate scope displayed by the Rh(III) catalysis, we performed mechanistic studies to delineate its mode of action (Scheme 3). To this end, the competition experiments between differently substituted indoles indicated that electron-rich indoles were preferentially converted, suggesting they were better substrates than electron-poor indoles.

Due to its importance for further functionalization of the indole moiety, we attempted to deprotect the pyrimidyl group. As illustrated in Scheme 4, the deprotection was easily achieved by heating **3ga** with EtONa in DMSO for 2 h to provide free-NH indole derivative **4** as the final product in good yield (86%).[14] The obtained product is a very useful synthon, which can be transformed into a variety of natural products and pharmacophores such as Trp-P-2[15] and potent anti-inflammatory drug MK-7246,[16] respectively. Furthermore, C-2 alkenylation and then deprotection reactions could be performed on a 5.0-

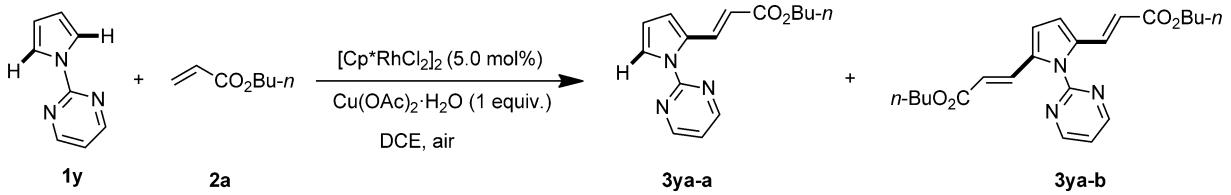




[a] The reaction was carried out using **1g** (0.25 mmol), **2a–c** (0.30 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), and $Cu(OAc)_2 \cdot H_2O$ (0.25 mmol) under air at 60 °C for 5 h.

Scheme 2. Scope of the reaction between indole **1g** and acrylic esters **2a–c**.[a]

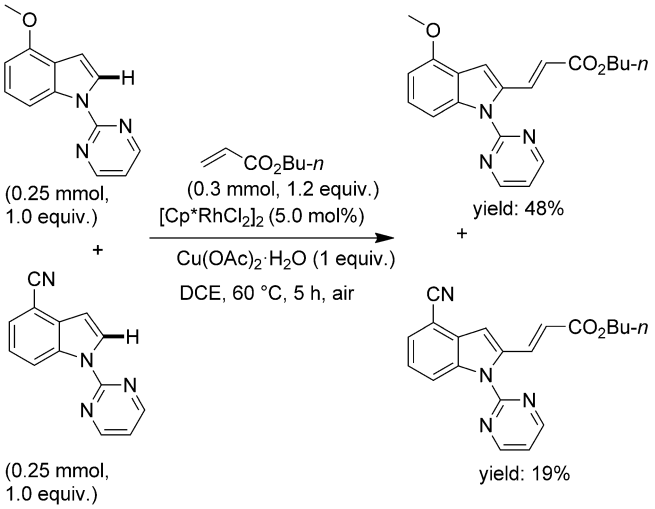
Table 3. C–H Alkenylation of *N*-(2-pyrimidyl)pyrrole.



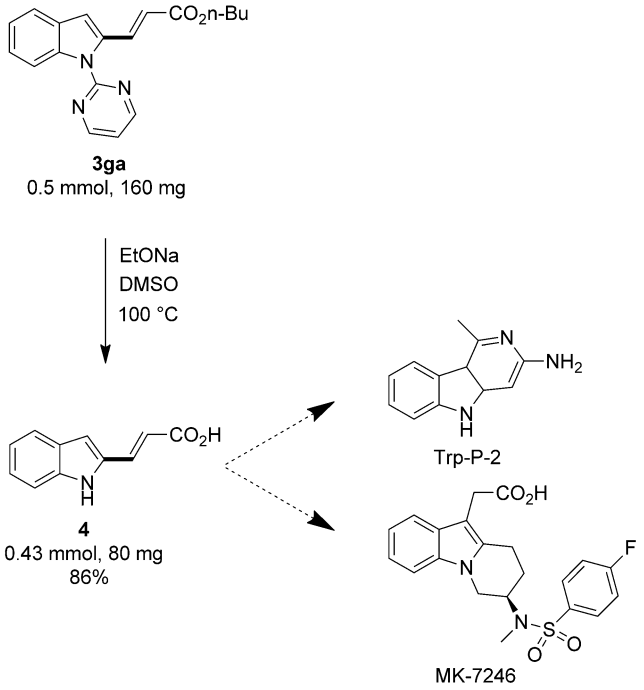
1y 2a 3ya-a 3ya-b

Entry	Temperature [°C]	Time [h]	Yield of **3ya-a**[b]	Yield of **3ya-b**[b]
1	60	1	21%	16%
2	60	2	11%	29%
3	60	5	trace	39%
4[c]	60	5	0	75%
5	r.t.	5	0	0

[a] *Reaction conditions:* **1y** (0.25 mmol), **2a** (0.30 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (0.25 mmol), in DCE (1.0 mL) under air.
[b] Isolated yields.
[c] 3.0 equiv. of **2a** (0.75 mmol) were used in the reaction.



Scheme 3. Competition experiment.



Scheme 4. Deprotection and hydrolysis.

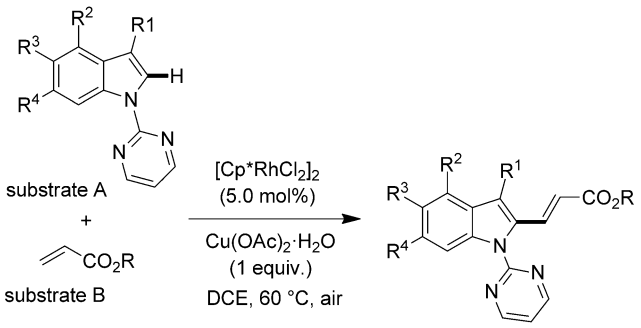
mmol scale without any significant decrease in the corresponding product yield.[17]

In conclusion, a mild, versatile, and highly efficient Rh(III)-catalyzed C-2 alkenylation strategy for indoles has been demonstrated. This protocol strongly relies on the use of the easily attachable pyrimidyl group as the metal-directing group. To the best of our knowledge, this is the first report of such an Rh(III)-catalyzed direct C-2 alkenylation of *N*-(2-pyrimidyl)-indoles with alkyl acrylates. The remarkable features of this methodology including good product yields, wide tolerance of various functional groups, and excellent regio-/site-specificities, thus render this methodology as a highly versatile and atom-economical alternative to the existing methods for building the biologically important C-2-alkenylindole unit. Furthermore, the deprotection of the metal-directing pyrimidyl group is very simple and straightforward, which results in the C-2 acrylic acid-substituted free-NH indole, a valuable synthon for many important natural products and pharmacophore syntheses. The method reported here deepens the understanding of Rh(III)-mediated catalytic behavior and will promote future applications in the synthesis of more biologically important indole derivatives.

Experimental Section

General Procedure for C–H Activation Reaction

The mixture of $[Cp^*RhCl_2]_2$ (7.8 mg, 0.0125 mmol, 0.05 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (50 mg, 0.25 mmol, 1.0 equiv.), substrate A (0.25 mmol, 1.0 equiv.), substrate B (0.30 mmol, 1.2 equiv.) and DCE (1 mL) was stirred at 60 °C for 5 h under air. The resulting mixture was cooled to room temperature and subjected to silica gel column chromatography directly to give the desired product.



Acknowledgements

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