C–H Bond Activation Hot Paper

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Stereoselective Synthesis of Tetrasubstituted Alkenes via a Cp*Co^{III}-Catalyzed C–H Alkenylation/Directing Group Migration Sequence

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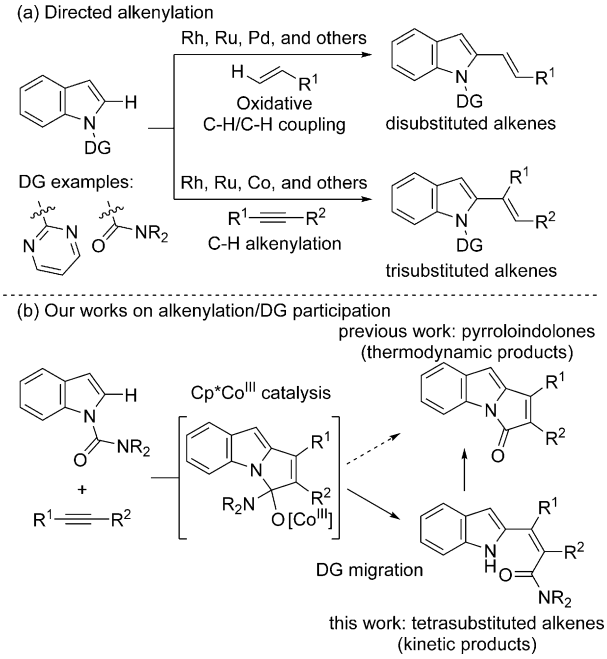
Abstract: *A highly atom economical and stereoselective synthesis of tetrasubstituted α,β-unsaturated amides was achieved by a Cp*Co^{III}-catalyzed C–H alkenylation/directing group migration sequence. A carbamoyl directing group, which is typically removed after C–H functionalization, worked as an internal acylating agent and migrated onto the alkene moiety of the product. The directing group migration was realized with the Cp*Co^{III} catalyst, while a related Cp*Rh^{III} catalyst did not promote the migration process. The product was further converted into two types of tricyclic compounds, one of which had fluorescent properties.*

Tetrasubstituted alkenes are found in many biologically active molecules[1] and natural products.[2] They are also important synthetic intermediates for the synthesis of highly congested vicinal stereogenic carbon centers by various difunctionalization reactions of tetrasubstituted alkenes.[3–5] Stereoselective synthesis of all-carbon tetrasubstituted alkenes, however, remains a great challenge because of their congested nature and difficulties in controlling stereoselectivity. General strategies for their construction involve carbometalation of internal alkynes and successive cross-coupling reactions or addition to electrophiles.[6] Although remarkable advances have been made in these strategies, the use of stoichiometric organometallic reagents is still inevitable.[7] On the other hand, transition-metal-catalyzed C–H bond functionalizations[8] have emerged as atom-[9] and step-economical[10] methods for synthesizing di- and trisubstituted alkenes.[11] These reactions generally proceed by either a transition-metal-catalyzed C–H/C–H oxidative coupling reaction with alkenes or a redox-neutral alkyne insertion at C–H bonds without stoichiometric amounts of organometallic reagents (Scheme 1a). In the latter reactions, proto-demetalation or reductive elimination to form an alkenyl–H bond occurs after alkyne insertion, making the formation of the fourth C–C bond difficult.



Scheme 1. a) Previous work: di- and trisubstituted alkene synthesis by C–H functionalization b) This work: synthesis of tetrasubstituted olefins by C–H alkenylation/donating group (DG) migration sequence.

We previously reported the Cp*Co^{III}-catalyzed[12–15] synthesis of pyrroloindolones, in which C–H alkenylation and successive intramolecular nucleophilic addition to a carbamoyl directing group of indole proceeded without proto-demetalation (Scheme 1b, previous work).[15] During the course of our further studies of this reaction, we found that the tetrasubstituted alkene was formed as a kinetically controlled product (Scheme 1b, this work). The obtained tetrasubstituted alkene, which is difficult to access stereoselectively by other methods, is considered to be formed by directing group migration.[16] Herein, we report the optimized conditions for this atom economical directing group migration process, in which the carbamoyl group works not only as a directing group but also as an internal acylating agent.

Optimization studies using *N*-morpholinocarbamoyl indole **2a** and alkyne **3a** under Cp*Co^{III}/KOAc catalysis are summarized in Table 1. The best reaction conditions for the synthesis of pyrroloindolone **5** using Cp*Co^{III}-arene catalyst

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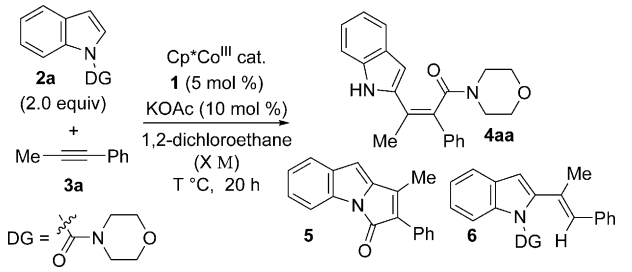
Table 1: Optimization studies and control experiments.[a]



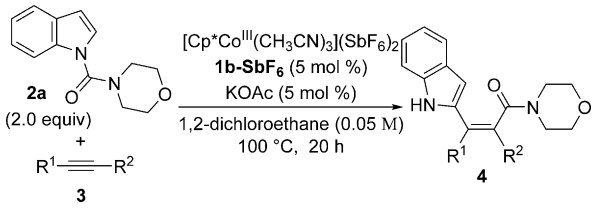
Entry	Cat.[b]	X [M]	*T* [°C]	Yield [%][c]		
				4aa	**5**	**6**
1	**1a**	0.10	130	0	82	10
2	**1a**	0.10	100	37	23	22
3	**1a**	0.05	100	40	< 1	10
4	**1b-BF$_4$**	0.05	100	50	5	6
5	**1b-PF$_6$**	0.05	100	50	4	6
6	**1b-SbF$_6$**	0.05	100	69	7	5
7[d]	**1b-SbF$_6$**	0.05	100	80 (74)[e]	5	6
8[f]	**1b-SbF$_6$**	0.05	100	10	0	0
9[d]	**1c (Rh)**	0.05	100	0	0	0
10[g]	**1c (Rh)**	0.05	100	0	0	3
11[h]	**1c (Rh)**	0.05	100	0	0	8

[a] Reaction conditions: **2a** (0.40 mmol) and **3a** (0.20 mmol). [b] **1a** = [Cp*Co(C_6H_6)]$(PF_6)_2$, **1b-X** = [Cp*Co($CH_3CN)_3$]X_2, **1c** = [Cp*Rh-($CH_3CN)_3$]$(SbF_6)_2$. [c] Determined by ^{1}H NMR analysis with an internal standard. [d] KOAc (5 mol%) was used. [e] Isolated yield of **4aa** after purification by silica gel column chromatography. [f] Reaction without KOAc. [g] CsOAc (5 mol%) was used instead of KOAc. [h] CsOPiv (5 mol%) was used instead of KOAc.

1a are shown in entry 1, in which C–H alkenylation, successive intramolecular nucleophilic addition to the carbamoyl directing group, and elimination of an amine, proceed with high selectivity. When the reaction temperature was decreased to 100 °C, the yield of **5** dropped to 23 % along with the alkenylation product **6** (22 %). After careful analysis of the reaction mixture, we identified **4aa** as a major product (37 % yield, entry 2). To decelerate the undesired protodemetalation leading to **6**, the concentration of **3a** was decreased to 0.05 M and the desired alkene **4aa** was obtained in 40 % yield with moderate selectivity. Although further minor modification of the reaction conditions was unfruitful, screening of Cp*Co^{III} catalysts led to improvement (entries 4–6). For our desired reaction, the [Cp*Co^{III}($CH_3CN)_3$]X_2 catalysts[17] **1b-X** had higher reactivity and selectivity than the Cp*Co^{III}-arene catalyst **1a**, and the best catalyst **1b-SbF$_6$** afforded 69 % yield (entry 6). We screened the reaction conditions again using **1b-SbF$_6$** and determined that 5 mol % KOAc was optimal (entry 7) to give **4aa** in 80 % yield (74 % isolated yield). The reactivity dramatically decreased without a catalytic amount of KOAc (entry 8), indicating that KOAc had an important role in efficient C–H bond cleavage by a concerted metalation–deprotonation mechanism.[18] We also confirmed that Cp*Rh^{III} catalyst **1c**[19,20] did not promote the desired directing group migration, and only a small amount of the alkenylated product **6** was obtained, even after screening of the carboxylate additives (entries 9–11). These results indicate that high nucleophilicity of the C–Co bond is essential.[12a,15]

The optimal reaction conditions were then applied to various alkynes, as summarized in Table 2. The C–H alkenylation/donating group (DG) migration sequence of indole **2a** proceeded well with various aryl/alkyl alkynes that

Table 2: Substrate scope of C–H alkenylation/DG migration with alkynes.[a]



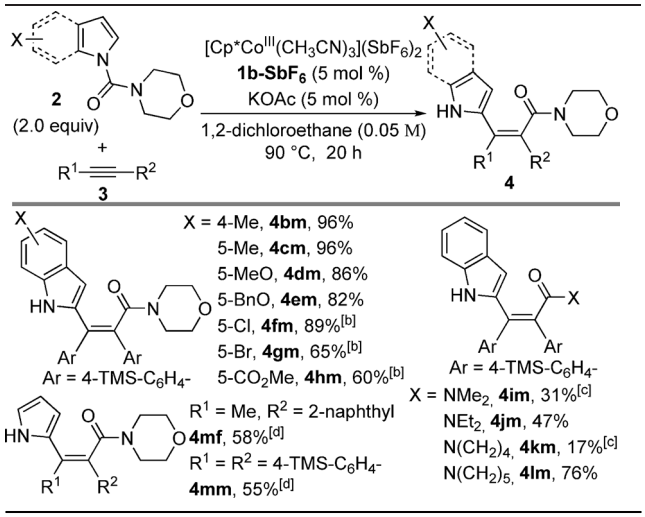
Entry	R^1	R^2	**3**	**4**	Yield[b] [%]
1	Me	Ph	**3a**	**4aa**	74
2	Me	4-Me-C_6H_4	**3b**	**4ab**	55
3[c]	Me	4-Cl-C_6H_4	**3c**	**4ac**	77
4[c]	Me	4-Br-C_6H_4	**3d**	**4ad**	58
5[c]	Me	4-CO_2Et-C_6H_4	**3e**	**4ae**	74
6	Me	2-naphthyl	**3f**	**4af**	71
7	Me	6-MeO-naphth-2-yl	**3g**	**4ag**	69
8	Et	Ph	**3h**	**4ah**	76
9	Pr	Ph	**3i**	**4ai**	69
10[d]	Ph	Ph	**3j**	**4aj**	87
11[d]	4-Me-C_6H_4	4-Me-C_6H_4	**3k**	**4ak**	85
12[d]	4-Br-C_6H_4	4-Br-C_6H_4	**3l**	**4al**	71
13[d]	4-TMS-C_6H_4	4-TMS-C_6H_4	**3m**	**4am**	99
14	TBDPSO$(CH_2)_3$-	Ph	**3n**	**4an**	76
15	Bu	2-thienyl	**3o**	**4ao**	70
16	TMS	Ph	**3p**	**4ap**	54
17	Pr	Pr	**3q**	**4aq**	0
18	H	Ph	**3r**	**4ar**	0

[a] Reaction conditions: **1b-SbF$_6$** (5 mol%), KOAc (5 mol%), **2a** (0.40 mmol), **3** (0.20 mmol), 1,2-dichloroethane (4.0 mL), Ar atmosphere at 100 °C, unless otherwise noted. [b] Isolated yields of **4** (single regioisomer) after purification by silica gel column chromatography. [c] 1,2-dichloroethane (6.0 mL, 0.033 M) [d] 90 °C.

have electron-donating and electron-withdrawing substituents on the aromatic rings, and products were obtained in 55–77 % yield (entries 1–7). The indicated products were obtained as single regioisomers in all cases. Good reactivities and high selectivities were also observed with other alkyl substituents, such as ethyl or propyl on alkynes (entries 8, 9). Diaryl-substituted alkynes were also compatible to give the desired products in 71–99 % yield (entries 10–13). A functionalized alkyne **3n** bearing a silyl ether unit also gave **4an** in 76 % yield without deprotection (entry 14). An alkyne **3o** with a thiophene ring gave tetrasubstituted alkene **4ao**, containing two different heteroaromatic rings, in 70 % yield (entry 15). While alkyne **3p** protected with trimethylsilyl (TMS) group resulted in **4ap** in a moderate yield (entry 16); dialkylalkyne **3q** afforded the alkenylation product **6aq** exclusively (entry 17). No reaction proceeded with a terminal alkyne **4r** (entry 18).

The scope of indoles is summarized in Table 3. Both electron-donating and electron-withdrawing substituents were compatible, and various 4- or 5-substituted indoles resulted in 60–96 % yield (**4bm–4hm**). Indoles with other

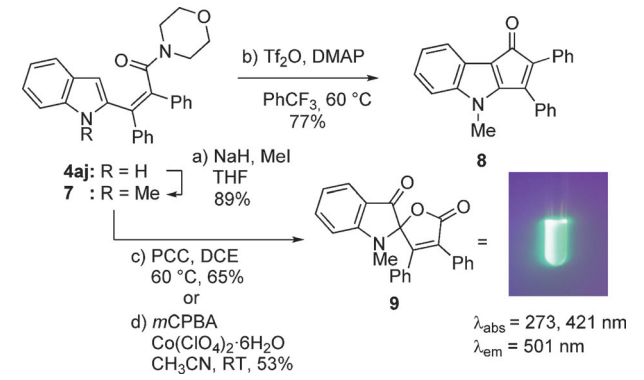
Table 3: Substrate scope of C–H alkenylation/DG migration with indoles and pyrroles.[a]



[a] Reaction conditions: **1b-SbF$_6$** (5 mol%), KOAc (5 mol%), **2** (0.40 mmol), **3** (0.20 mmol), 1,2-dichloroethane (4.0 mL), Ar atmosphere at 90°C, unless otherwise noted. Isolated yields of **4** (single regioisomer) after purification by silica gel column chromatography are listed. [b] Reaction conditions: 80°C, 12 h. [c] 100°C [d] Reaction conditions: KOAc (10 mol%), 1,2-dichloroethane (2.0 mL), 100°C.

carbamoyl directing groups also gave the corresponding tetrasubstituted alkenes **4im**–**4lm** although the reactivity was significantly affected by the structure of the directing group. Moreover, *N*-carbamoyl pyrrole **4m** also underwent the desired alkenylation/DG migration reaction to give pyrrole-substituted tetrasubstituted alkenes **4mf** and **4mm**. The DG migration during the first C–H functionalization inhibits the second functionalization of another C–H bond of the pyrrole ring.

The product **4aj** was further converted to two different tricyclic compounds, **8** and **9** (Scheme 2). After *N*-methylation (**7**), treatment with trifluoromethanesulfonic anhydride (Tf_2O) and 4-dimethylaminopyridine (DMAP)[21] promoted electrophilic cyclization at the C3 position to afford **8**. On the other hand, the spirocyclic compound **9** was obtained by oxidation using pyridinium chlorochromate (PCC)[22] or 3-chloroperbenzoic acid (*m*CPBA)/$Co(ClO_4)_2$.[23] Spirocycle **9** exhibited green fluorescence with a maximum emission wavelength of 501 nm. Our synthetic method is expected to provide easy access to various substituted analogues of this fluorescent molecule.



Scheme 2. Transformation of **4aj** into tricyclic compounds.

A plausible catalytic cycle involving the Cp*Co^{III} complex in the presence of KOAc is shown in Figure 1. As the initial step, three acetonitrile ligands dissociate from [Cp*Co^{III}-$(CH_3CN)_3$]$(SbF_6)_2$, and ligand exchange with acetate

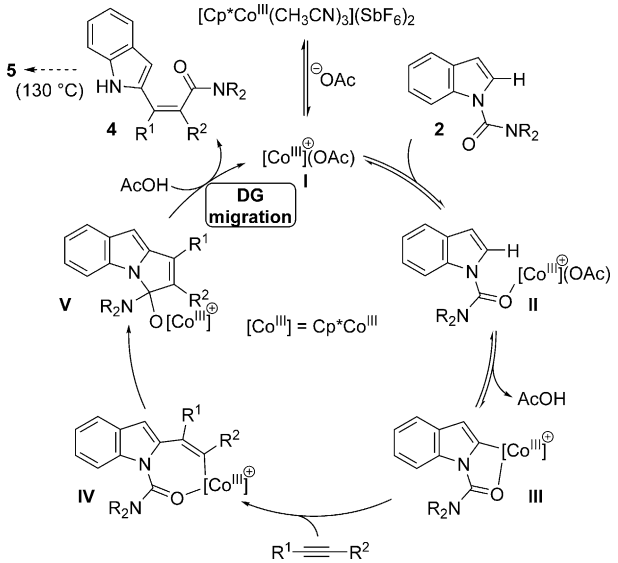


Figure 1. Plausible catalytic cycle of C–H alkenylation/DG migration sequence with indole and alkyne.

generates a catalytically active monocationic species **I**. After coordination of the carbamoyl group of indole **2** (**II**), regioselective C–H metalation at the C2 position occurs by a concerted metalation–deprotonation (CMD) mechanism[18] to afford the indolyl–Co species **III**. The result without KOAc (Table 1, entry 8) indicates that an electrophilic aromatic substitution (S_EAr) pathway and/or a CMD pathway with external base other than acetate competes, but an acetate-assisted CMD pathway is dominant under the optimal conditions. Insertion of alkyne **3** into the C–Co bond generates the key alkenyl–Co intermediate (**IV**). Nucleophilic addition of the C–Co bond to the carbamoyl directing group proceeds to afford the intermediate **V**. A low concentration was essential to avoid undesired proto-demetalation of **IV**, leading to **6**. Elimination of the indole results in DG migration, giving tetrasubstituted alkene **4**. Our previous report revealed that pyrroloindolone **5** is a major product at 130°C,[15] and we confirmed the formation of **5** from **4** at 130°C in the presence of **1a**/KOAc or KOAc (see Supporting Information). These data suggest that **4** is a kinetically favored primary product that undergoes cyclization, leading to a thermodynamically favored product **5**; although direct formation of **5** from **V** at 130°C is also possible to some extent.

In conclusion, the Cp*Co^{III}-catalyzed directing group migration reaction of carbamoyl-protected indoles/pyrrole and alkynes afforded tetrasubstituted alkenes **4** in 17–99% yield with complete stereoselectivity and high atom economy

under carefully optimized reaction conditions. The product was easily converted to tricyclic compound **8** and a fluorescent spirocycle **9**.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H activation · cobalt · first row transition metals · homogeneous catalysis · indoles

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Communications

C–H Bond Activation

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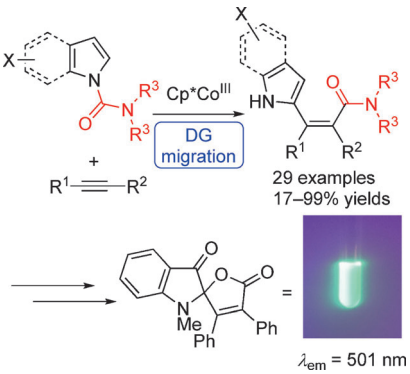
Stereoselective Synthesis of Tetrasubstituted Alkenes via a Cp*Co^{III}-Catalyzed C–H Alkenylation/Directing Group Migration Sequence



Tetrasubstituted alkenes were stereoselectively synthesized by a Cp*Co^{III}-catalyzed C–H alkenylation/directing group migration sequence, within which a carbamoyl functional group operates as a directing group and an internal acylating agent. A fluorescent spirocyclic molecule was generated from the resulting alkene.