Copper-catalyzed asymmetric addition of arylboronates to isatins: a catalytic cycle involving alkoxocopper intermediates†

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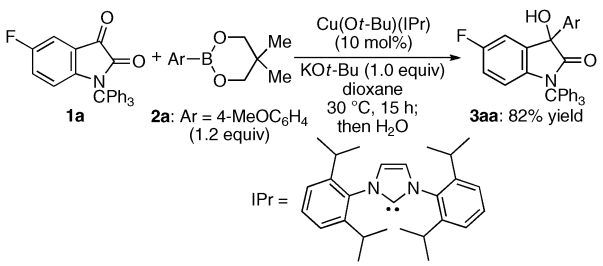
Received 28th May 2010, Accepted 8th July 2010
DOI: 10.1039/c0cc01635g

A copper-catalyzed addition of arylboronates to isatins has been developed to give 3-aryl-3-hydroxy-2-oxindoles under mild conditions. The catalytic cycle of this process has been examined through a series of stoichiometric reactions and an effective asymmetric variant has also been described by the use of a chiral *N*-heterocyclic carbene ligand.

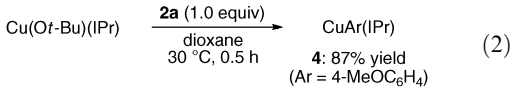
Copper-catalyzed carbon–carbon bond forming reactions using organometallic reagents are powerful tools for efficient construction of organic compounds, and highly reactive nucleophiles such as Grignard reagents,[1] diorganozincs,[2] and triorganoaluminiums[2a,b] are typically employed. In contrast, the use of milder nucleophiles such as organosilicon[3] and organoboron[4–6] reagents has been much less studied, although employment of organoboronic acids and their derivatives would be highly attractive in view of the availability, stability, and ease of handling of these reagents. Several copper-catalyzed carbon–carbon bond formations using organoboronic acid derivatives have been reported,[4,5] but those with absolute stereocontrol in the product formation are quite limited.[3d,5] In this context, here we describe that alkoxocopper complexes can efficiently catalyze the addition of arylboronic acid esters to isatins to give 3-aryl-3-hydroxy-2-oxindoles, which constitute a useful class of compounds that can be found in various biologically active molecules,[7] and that the use of a chiral *N*-heterocyclic carbene ligand leads to the development of an effective asymmetric variant.[8,9]

Because copper–*N*-heterocyclic carbene complexes[10] are known to display high catalytic activity for the reactions of carbonyl compounds,[11] including addition of organoboronates to carbon dioxide,[4a] we initially employed Cu(O*t*-Bu)(IPr)[12] as a catalyst (10 mol%) for the reaction of isatin **1a** with 4-methoxyphenylboronate **2a** in the presence of 1.0 equiv. of KO*t*-Bu in dioxane at 30 °C (eqn (1)). Under these conditions, the reaction smoothly proceeded to give the desired addition product (**3aa**) in 82% yield after aqueous workup. It is worth noting that the reaction became very sluggish in the absence of KO*t*-Bu, giving **3aa** only in 22% yield under otherwise the same conditions.

The catalytic cycle for the present reaction was probed by conducting a series of stoichiometric reactions as follows.[4a] (1) A reaction of Cu(O*t*-Bu)(IPr) with **2a** in dioxane at 30 °C cleanly produced Cu(4-MeOC$_6$H$_4$)(IPr) (**4**) in 87% yield (eqn (2)), as reported by Hou and coworkers.[4a] (2) Arylcopper **4** thus obtained underwent insertion of isatin **1a** in dioxane at 30 °C to give alkoxocopper complex **5** quantitatively (eqn (3)).[13] Recrystallization of this complex from *n*-Bu$_2$O/pentane afforded crystals suitable for X-ray analysis as shown in Fig. 1.[14] (3) Unlike Cu(O*t*-Bu)(IPr), alkoxocopper **5** did not undergo transmetalation with 1.0 equiv. of **2a** in dioxane at 30 °C (eqn (4)). The lack of transmetalation ability of **5** with **2a** in comparison to Cu(O*t*-Bu)(IPr) may be attributed to the very bulky alkyl group in the alkoxy moiety, which is also indicated by the X-ray crystal structure in Fig. 1.[15] (4) In contrast, 82% of complex **5** was converted to Cu(O*t*-Bu)(IPr) in 0.5 h by treating it with 1.0 equiv. of KO*t*-Bu in dioxane at 30 °C (eqn (4)), and the results of eqn (4) can well explain the necessity of KO*t*-Bu for the catalytic reaction in eqn (1). (5) Furthermore, both complexes **4** and **5** effectively catalyzed the reaction of **1a** with **2a**.



(1)



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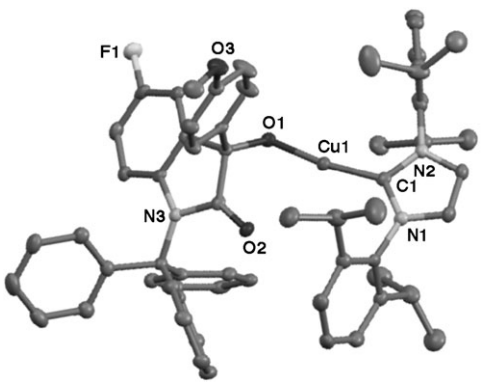

Fig. 1 X-Ray crystal structure of **5** (hydrogen atoms are omitted for clarity). Selected bond lengths (Å) and an angle (°): Cu1–C1 1.857(3), Cu1–O1 1.825(2); C1–Cu1–O1 170.75(11).

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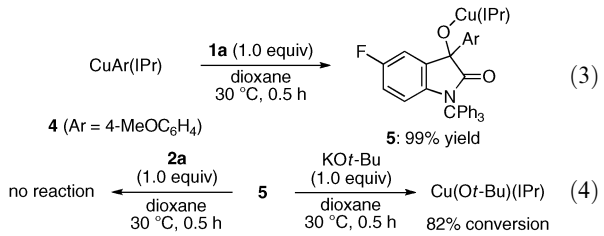
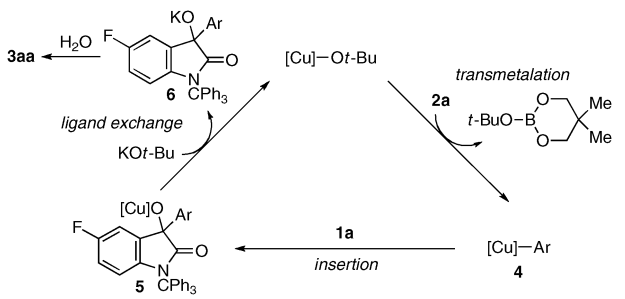
† Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data. CCDC 775043 and 775074. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc01635g



On the basis of these experiments, a proposed catalytic cycle for the reaction in eqn (1) is illustrated in Scheme 1. Thus, Cu(O*t*-Bu)(IPr) undergoes transmetalation with arylboronate **2a** to give arylcopper species **4**. Insertion of isatin **1a** to arylcopper **4** then gives alkoxocopper **5**, which reacts with KO*t*-Bu to regenerate Cu(O*t*-Bu)(IPr) along with primary product **6**. Final product **3aa** is obtained from **6** after aqueous workup.

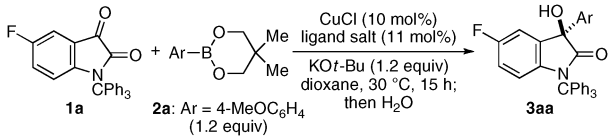
Because the step from **4** to **5** in Scheme 1 creates a tetra-substituted carbon stereocenter, we began to develop an asymmetric variant by employing chiral *N*-heterocyclic carbene (NHC) ligands.[16,17] Although the reaction of **1a** with **2a** smoothly proceeded by the use of C_2-symmetric (*R*,*R*)-**7**[18] as the ligand precursor, the enantioselectivity of product **3aa** was only 8% ee (Table 1, entry 1). In contrast, C_1-symmetric NHC salt (*S*)-**8a**[19] having a phenylglycinol-derived tether significantly improved the enantioselectivity (62% ee; entry 2), and the change of substituent on the tether from phenyl to isopropyl ((*S*)-**8b**, 83% ee; entry 3) or *tert*-butyl ((*S*)-**8c**, 88% ee; entry 4) gave higher enantioselectivity. The structurally similar NHC salt (*S*)-**9** having a methoxy group instead of a hydroxy group displayed much lower enantioselectivity (14% ee; entry 5). With regard to the substituent on the other nitrogen atom of **8**, a 2,6-dimethylphenyl group turned out to be optimal. Thus, the decrease ((*S*)-**8d**) or increase ((*S*)-**8e** and (*S*)-**8f**) of the steric bulk of the 2,6-substituents led to erosion of ee (entries 6–8). It is worth noting that the catalyst loading of Cu–(*S*)-**8c** can be lowered to 5 mol%, although a prolonged reaction time is required (71% yield, 88% ee; entry 9).

Under the conditions using (*S*)-**8c** as the ligand precursor, not only **1a** but also several other isatins (**1b–1e**) can be employed in the reaction with 4-methoxyphenylboronate **2a** to give **3** with similar efficiency (67–83% yield, 85–89% ee; Table 2, entries 1–5). With respect to the nucleophilic component, various aryl groups including 2-naphthyl and 3-thienyl are effectively incorporated to isatins **1** with high enantioselectivity (74–94% yield, 86–92% ee; entries 6–12). The addition of a 2-tolyl or 1-cyclohexenyl group, however, results in moderate enantioselectivity (72–74% yield, 67–68% ee; entries 13 and 14).



Scheme 1 Proposed catalytic cycle for the copper-catalyzed addition of **2a** to **1a** ([Cu] = Cu(IPr), Ar = 4-MeOC$_6$H$_4$).

Table 1 Copper-catalyzed asymmetric addition of arylboronate **2a** to isatin **1a**: ligand effect



Entry	Ligand salt	Yield (%)[a]	ee (%)[b]
1	(*R*,*R*)-**7**	80	8
2	(*S*)-**8a**	66	62
3	(*S*)-**8b**	67	83
4	(*S*)-**8c**	**80**	**88**
5	(*S*)-**9**	73	14
6	(*S*)-**8d**	67	31
7	(*S*)-**8e**	71	78
8	(*S*)-**8f**	67	52
9[c]	(*S*)-**8c**	71	88

[a] Isolated yield. [b] Determined by chiral HPLC on a Chiralcel OD-H column with hexane/2-propanol = 90/10. [c] The reaction was conducted for 36 h in the presence of 5 mol% of CuCl and 5.5 mol% of (*S*)-**8c**.

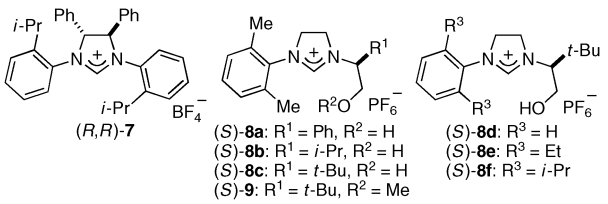
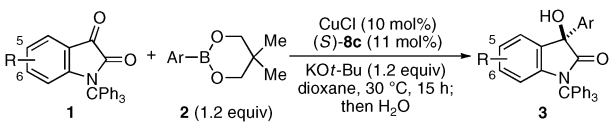


Table 2 Copper-catalyzed asymmetric addition of arylboronates **2** to isatins **1:** scope

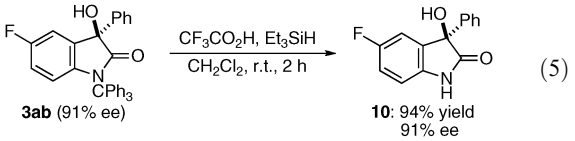


Entry	**1** (R)	**2** (Ar)	Product	Yield (%)[a]	ee (%)[b]
1	**1a** (5-F)	**2a** (4-MeOC$_6$H$_4$)	**3aa**	80	88
2	**1b** (5-Me)	**2a**	**3ba**	67	85
3	**1c** (6-Br)	**2a**	**3ca**	83	89
4	**1d** (6-Cl)	**2a**	**3da**	70	89
5[c]	**1e** (H)	**2a**	**3ea**	76	85
6	**1a**	**2b** (Ph)	**3ab**	74	91
7	**1c**	**2b**	**3cb**	83	92
8	**1d**	**2b**	**3db**	87	92
9	**1d**	**2c** (4-MeC$_6$H$_4$)	**3dc**	87	92
10	**1a**	**2d** (4-ClC$_6$H$_4$)	**3ad**	78	86 (*R*)
11	**1a**	**2e** (2-naphthyl)	**3ae**	85	86
12	**1a**	**2f** (3-thienyl)	**3af**	94	87
13	**1a**	**2g** (2-MeC$_6$H$_4$)	**3ag**	74	68
14	**1a**	**2h** (1-cyclohexenyl)	**3ah**	72	67

[a] Isolated yield. [b] Determined by chiral HPLC on a Chiralcel OD-H column with hexane/2-propanol. [c] The reaction was conducted for 36 h.

The absolute configuration of product **3ad** was determined to be (*R*) by X-ray crystallographic analysis.[14] The trityl group on the nitrogen of product **3ab** can be readily removed with retention of the enantiomeric purity. Thus, treatment of **3ab** (91% ee) with CF_3CO_2H in the presence of triethylsilane

provides deprotected oxindole **10** in 94% yield with 91% ee (eqn (5)).[20]



(5)

In summary, we have developed a copper-catalyzed addition of arylboronates to isatins to give 3-aryl-3-hydroxy-2-oxindoles under mild conditions. The catalytic cycle of this process has been examined through a series of stoichiometric reactions and an effective asymmetric variant has also been described by the use of a chiral *N*-heterocyclic carbene ligand.

Support has been provided in part by a Grant-in-Aid for Young Scientists (B), the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by Mitsubishi Tanabe Pharma Corporation. K.T. thanks JSPS for a fellowship.

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