ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 6372–6374

www.rsc.org/chemcomm

COMMUNICATION

Borderline metal-catalyzed carboarylation of alkynylarenes using *N*,*O*-acetals†

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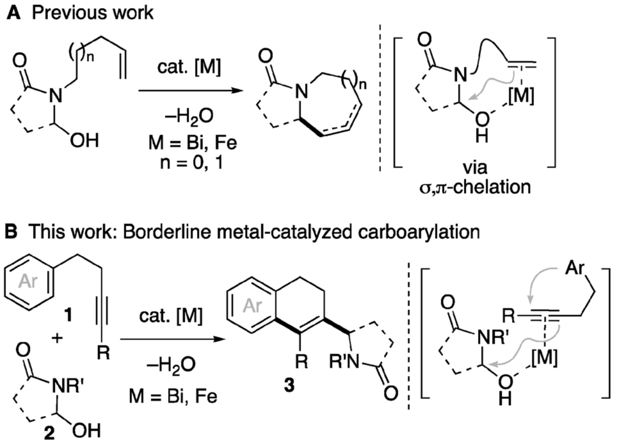
Received 17th April 2012, Accepted 8th May 2012
DOI: 10.1039/c2cc32715e

Borderline metal catalysts, $Bi(OTf)_3$ and $Fe(OTf)_3$, were proven to work as dual activators for alkynes and *N*,*O*-acetals *via* σ,π-chelation, which achieved a new carboarylation reaction of alkynylarenes with *N*,*O*-acetals.

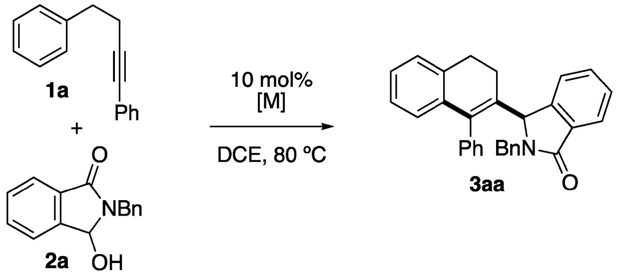
N-Acyliminium ions can be easily derived from *N*,*O*-acetals, and are widely recognized as useful synthetic intermediates for the construction of carbon–carbon bonds due to their high electrophilic character.[1] These reactions typically employ electron-rich aromatic nucleophiles as well as allyl, vinyl, and alkynyl metal species,[2] whereas unactivated olefins and alkynes are less reactive to *N*-acyliminium ions under catalytic conditions.[3] Recently, we have demonstrated a borderline metal-catalyzed cyclization of alkenyl *N*,*O*-acetals to afford a diverse set of nitrogen-containing heterocycles (Scheme 1A).[4] In the cyclization, the alkene and the hydroxyl group of *N*,*O*-acetal were dually activated by Fe or Bi catalysts *via* σ,π-chelation,[5] allows the two reaction sites to be close enough to interact with each other.[6] In contrast, we have also described a Fe- or Bi-catalyzed hydroarylation of alkynylarenes, in which these catalysts were able to activate the alkyne moiety.[7] With this in mind, we envisaged that the σ,π-chelation might be also applied to the dual activation of alkynes and *N*,*O*-acetals. Herein, we report borderline metal-catalyzed carboarylation of alkynylarenes **1** with *N*,*O*-acetal **2** (Scheme 1B).



Scheme 1

To prove the viability of the carboarylation, we first examined the reaction of 1,4-diphenylbut-1-yne (**1a**) with *N*-benzyl-3-hydroxyisoindoline-1-one (**2a**)[8] by using various Lewis acid catalysts (Table 1). When **1a** was treated with 1.1 equivalents of **2a** in the presence of $Bi(OTf)_3$ or $Fe(OTf)_3$ catalysts (10 mol%) in 1,2-dichloroethane (DCE) for 5 h at 80 °C, the carboarylated product **3aa** was obtained in 96% or 95% yields, respectively (entries 1 and 2). Although $Cu(OTf)_2$, $Fe(OTf)_2$, and $Zn(OTf)_2$ also afforded **3aa**, the yields were much lower than Bi and Fe catalysts (entries 3–5). $PtCl_2$ and AgOTf provided negligible yields of **3aa**, wherein a large amount of both substrates remained unchanged after the reaction (entries 6 and 7). If the generation of the iminium ion is a driving force to direct this carboarylation, it would

Table 1 Screening of catalysts[a]



Entry	Catalyst	Time/h	Yield[b]/%
1	$Bi(OTf)_3$	5	96
2	$Fe(OTf)_3$	5	95
3	$Cu(OTf)_2$	5	58
4	$Fe(OTf)_2$	5	50
5	$Zn(OTf)_2$	18	30
6	$PtCl_2$	18	12
7	AgOTf	18	11
8	$Ga(OTf)_3$	18	20
9	$Yb(OTf)_3$	18	16
10	$Sc(OTf)_3$	18	14
11	$AlCl_3$	18	0
12	$BF_3{\cdot}OEt_2$	18	0
13	TfOH	18	5

[a] Conditions: **1a** (0.5 mmol), **2a** (0.55 mmol). [b] NMR yield.

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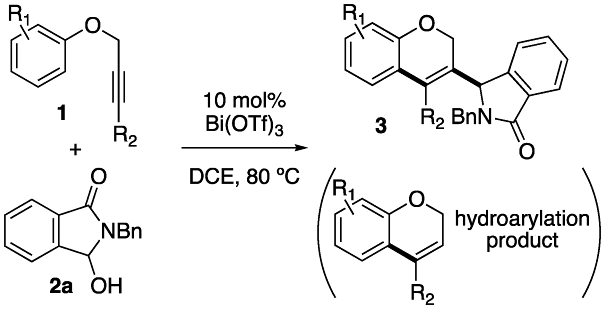
† Electronic supplementary information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/c2cc32715e

occur with other Lewis acid catalysts having high affinity to the hydroxyl group of **2a**. But, no or negligible yields of the product were detected by Ga(OTf)$_3$, Yb(OTf)$_3$, Sc(OTf)$_3$, AlCl$_3$, BF$_3$·OEt$_2$, and TfOH catalysts (entries 8–13). Moreover, to confirm the occurrence of the iminium ion in entries 1 and 13, the reaction of **1a** with **2a** in the presence of allyltrimethylsilane (3.0 equiv.) using TfOH or Bi(OTf)$_3$ catalyst was carried out.[2b,9] As a result, TfOH afforded an allylated isoindolinone at the 3-position as a sole product, whereas Bi(OTf)$_3$ produced **3aa** in 60% yield with a trace amount of the allylated product. These results would indicate that Bi(OTf)$_3$ worked not only in the generation of the iminium, but also in the cyclization step. In addition, we confirmed that no reaction took place in the absence of the catalyst.

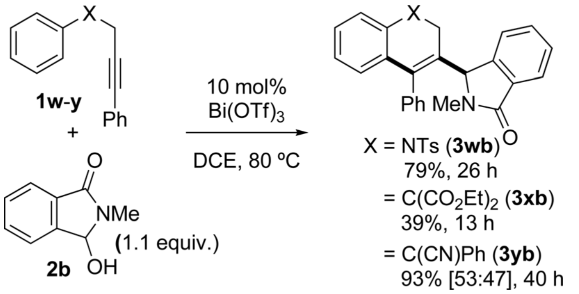
Next, with our optimized conditions in hand, we investigated the substituent effect of the aryl nucleophiles of the alkynylarenes **1** at the *para*-, *ortho*- and *meta*-positions. These results are summarised in Table 2. A wide range of electron-deficient aryl groups could successfully participate in the reaction, providing the corresponding carboarylated products **3** in good yields (entries 1–6 and 10–13). In contrast, electron-rich ones resulted in the formation of hydroarylation products (40–50% yields) with low yields of the desired products (entries 7–8 and 14–15). *meta*-Substituents produced the desired products as a mixture of two regioisomers of about 50 : 50 ratio (entries 16–20). An electron-rich terminal aryl group at the R^2-position accelerated the reaction (entry 2). An alkynylarene having an alkyl substituent at the R^2-position participated in the reaction, leading to a 4-alkylchromene adduct without detection of other cyclized products (entry 9). This transformation was not limited to alkynylarenes with ether and simple methylene tethers, nitrogen functionalized all-carbon tethers **1w–y** also took part in the reaction (eqn (1)). Moreover, the present reaction was compatible with other types of *N*,*O*-acetals like **2c** and **2d** to give the corresponding products **3ac** and **3ad**, respectively (eqn (2) and (3)). Particularly for **3ac**, the conversion of the phthalimidyl group to an amino one by Gabriel reaction could construct some ligands for histamine H$_1$-receptors.[10] Regarding the formation of **3ad**, it would be derived from the carboarylated product **3ad′** through an intramolecular hydroarylation of the olefin moiety.

Table 2 Substituent effect[a]

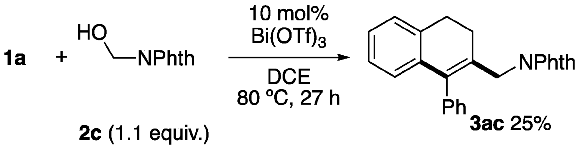


	Alkynylarenes 1				
Entry		R$_1$	R$_2$	Time/h	Yield of 3[b]/%
1	**1b**	4-CO$_2$Me	Ph	22 (57)[c]	58 (63)[c]
2	**1c**	4-CO$_2$Me	4-MeC$_6$H$_4$	4	84
3	**1d**	4-C(O)Ph	4-MeC$_6$H$_4$	5	68
4	**1e**	4-CN	Ph	30	67
5	**1f**	4-F	4-MeC$_6$H$_4$	5	84
6	**1g**	4-Br	Ph	24	99
7	**1h**	4-OMe	Ph	24	29
8	**1i**	4-Me	Ph	23	37
9	**1j**	4-Br	*n*-Bu	22	39
10	**1k**	2-NO$_2$	4-MeC$_6$H$_4$	5	58
11	**1l**	2-CN	4-MeC$_6$H$_4$	4	55
12	**1m**	2-F	4-MeC$_6$H$_4$	4	80
13	**1n**	2-Br	Ph	22	70
14	**1o**	2-OMe	Ph	24	27
15	**1p**	2-Me	Ph	25	11
16	**1q**	3-NO$_2$	Ph	24	70 [49 : 51][d]
17	**1r**	3-NO$_2$	4-MeC$_6$H$_4$	9	75 [52 : 48][d]
18	**1s**	3-CO$_2$Me	4-MeC$_6$H$_4$	5	82 [49 : 51][d]
19	**1t**	3-F	4-MeC$_6$H$_4$	7	81 [49 : 51][d]
20	**1u**	3-Br	4-MeC$_6$H$_4$	5	64 [48 : 52][d]

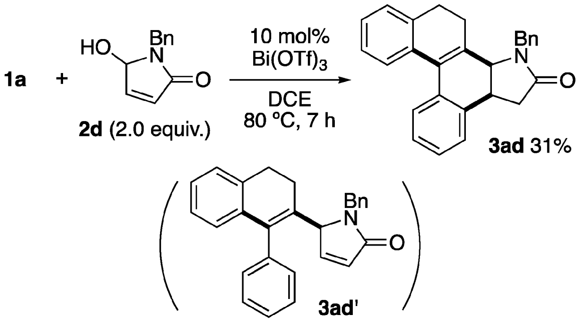
[a] Conditions: **1** (0.50 mmol), **2b** (0.55 mmol), Bi(OTf)$_3$ (0.05 mmol), DCE (1.0 mL), DCE (1.0 mL). [b] Isolated yield. [c] Fe(OTf)$_3$ was used instead of Bi(OTf)$_3$. [d] Regioisomer ratio of adducts at 2- and 6-positions.



(1)

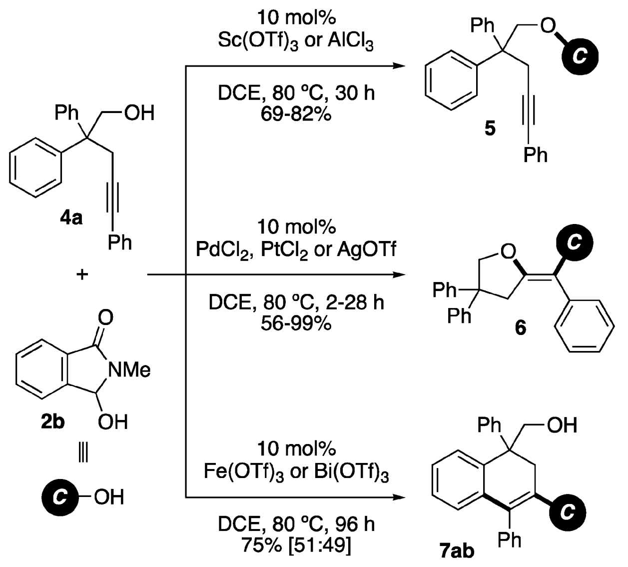


(2)

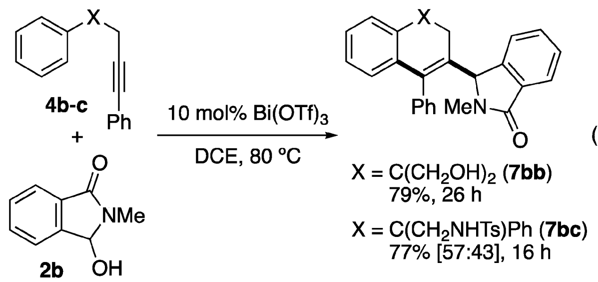


(3)

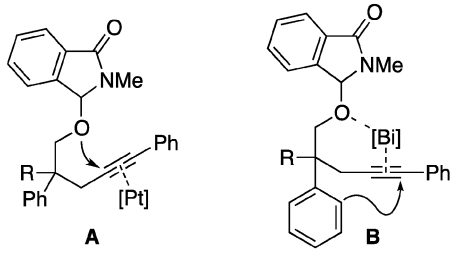
Notably, we observed different modes of reactions depending on the catalyst used in the reaction of an alkynylarene containing a hydroxyl group **4a** with *N*,*O*-acetal **2b** (Scheme 1). Thus, when hard Lewis acids such as Sc(OTf)$_3$ or AlCl$_3$ were used, condensation reaction of the hydroxyl group of **2b** with an alcoholic function of **4a** exclusively occurred to give **5** as a sole product. No other products were detected even after a longer reaction time (96 h). A reaction using soft Lewis acids like PdCl$_2$, PtCl$_2$, or AgOTf selectively afforded a carboalkoxylated product **6**. In contrast, borderline metal catalysts, Bi(OTf)$_3$ or



Scheme 2 Different reactivities of hard, soft, and borderline metal catalysts.



(4)



Scheme 3 Plausible intermediates in the Pt- and Bi-catalyzed reactions (Scheme 2, middle and bottom).

$Fe(OTf)_3$, afforded the carboarylation product **7ab** as a mixture of diastereomers. A similar chemoselectivity was repeated in the reaction of **4b** and **4c**, giving rise to **7bb** and **7cb**, respectively (eqn (4)). Monitoring of the $PtCl_2$- and $Bi(OTf)_3$-catalyzed reactions (Scheme 2; middle and bottom) showed the formation of **5** in the initial stage of these reactions. Furthermore, **5** could be converted into **6** or **7ab** with $PtCl_2$ or $Bi(OTf)_3$ catalysts, respectively. These results might indicate the presence of intermediates like **A** and **B** during the corresponding reactions as shown in Scheme 3. Thus, a high alkynophilicity of the platinum complex would give a π-complex **A**, which induced the attack of oxygen atom to the iminium ion across the alkyne. In contrast, the σ,π-interaction of the bismuth could provide a σ,π-chelated intermediate **B**, which would prefer the addition of aromatic nucleophile rather than that of the oxygen atom to afford the carboarylation products *via* the carbobismuthination of the alkyne[11] and a subsequent reaction of the C–Bi bond with the *N*-acyliminium ion.

In conclusion, we have demonstrated a novel carboarylation of alkynylarenes with the *N*-acyliminium ions generated from *N*,*O*-acetals by means of borderline metal catalysts like $Bi(OTf)_3$ and $Fe(OTf)_3$. This functionalization well tolerated a wide range of alkynylarenes, particularly, possessing non-protected heteroatom nucleophiles, and various *N*,*O*-acetals. In this reaction, the excellent catalytic activity of borderline metal complexes such as bismuth and iron would be attributable to the unique activation mode: σ,π-chelation. Further investigation of the mechanistic detail and the extension of this protocol to other types of double functionalization using *N*,*O*-acetals are in progress.

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. K.K. also acknowledges financial support from Kinki Invention Center and Furukawa Technical Foundation.

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