ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 2674–2676

www.rsc.org/chemcomm

COMMUNICATION

Iron-catalysed tandem cross-dehydrogenative coupling (CDC) of terminal allylic C(sp^3) to C(sp^2) of styrene and benzoannulation in the synthesis of polysubstituted naphthalenes†

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Received 24th November 2011, Accepted 12th January 2012
DOI: 10.1039/c2cc17330a

A novel iron-catalysed tandem cross-dehydrogenative coupling and benzoannulation process was developed for the synthesis of biologically and synthetically important polysubstituted naphthalene derivatives from simple 1,2-aryl-propenes and styrenes in moderate to good yields.

Since the pioneering work of Li and co-workers,[1] the direct formation of C–C bonds from different C–H bonds under oxidative conditions, termed cross-dehydrogenative coupling (CDC), has emerged as an exciting research area in organic synthesis.[2] The advantages of this strategy encompass high efficiency and environmental benignancy by avoiding the use of either organohalides/halide surrogates or organometallic reagents. Electrophilic substrates for these CDC reactions feature the presence of either heteroatoms (such as N, O and S)[1,3] or aryl/vinyl groups α- to the C(sp^3)–H[4] to be oxidized and coupled. C(sp^3)–H bonds adjacent to nitrogen have been used as the electrophilic components, with benzylic or allylic C(sp^3)–H bonds also attracting much attention due to their importance in organic synthesis. For example, Li and co-workers reported the first example of $FeCl_2$-catalyzed selective CDC of a benzylic C–H bond with 1,3-dicarbonyl compounds.[4a] Bao and co-workers described a DDQ mediated oxidative coupling of allylic C–H bonds with 1,3-dicarbonyl methylenic compounds.[4b] Shi and co-workers reported the direct functionalisation of benzylic C–H bonds with arene and vinyl acetates *via* iron-catalysis.[4c] It is noteworthy that, in most cases, the benzylic and allylic C–H bonds are doubly activated by diaryl (**S-I**) or aryl/vinyl groups (**S-II**) (Fig. 1), which might facilitate the formation of the active carbocation in the oxidative step. The C–C bond formation *via* the oxidative activation of allylic C–Hs without other activating components are mainly cyclic alkenes,[5] and those of an acyclic system have rarely been reported.[6] Recently, Shi and co-workers reported a direct allylic alkylation *via* a Pd(II)-catalysed allylic C–H activation regime and subsequent coupling with an active methylenic C–H bond. In their system,[7] exclusive terminal regioselectivities were observed when allylbenzene (**S-II**) was used as a substrate, and 1-aryl-1-propene (**S-III**) was completely inactive. Therefore, despite the success of C–heteroatom coupling through oxidative allylic C–H activation of monoactivated C–H bonds of 1-aryl-1-propene,[8] C–C bond formation *via* terminal allylic C–H (**S-III**) oxidative activation is still an extremely attractive but challenging task.

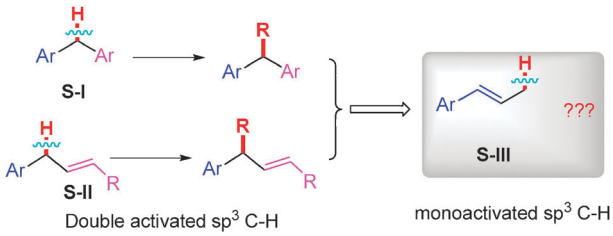

Fig. 1 Known CDC reactions of double activated sp^3 C–H.

Herein, a novel tandem cross-dehydrogenative coupling (CDC) of terminal allylic C(sp^3) to C(sp^2) of styrene and benzoannulation for the synthesis of polysubstituted naphthalenes is described. To the best of our knowledge, this methodology represents the first successful example of coupling of terminal allylic C(sp^3) to C(sp^2) of styrene *via* unconventional reaction mode.

Initially, model substrate **1a** with an allylic methyl group *syn* to a 1-phenyl group was designed to test the possibility of terminal allylic sp^3 C–H activation. With **1a** in hand, we planned to explore direct intramolecular CDC through a Friedel–Crafts type process to generate indene compound **2** upon allylic C–H bond activation. To our surprise, however, **1a** reacted smoothly in the presence of 20 mol% $FeCl_3$ to afford an unexpected product **3** in 41% yield, rather than the desired product **2** (Scheme 1).

A hypothetical reaction pathway was therefore proposed to account for the formation of product **3** (see ESI†), which can be considered as an iron-catalyzed CDC reaction of a mono-activated allylic C–H bond with an alkene.[4d,9] Encouraged by this finding, we further speculated about the possibility for the C–C bond coupling of *in situ* generated carbocation species with simple styrene instead of **1a**. Gratifyingly, when **1a** (1.0 equiv.) and styrene (1.5 equiv.) were mixed in nitromethane in the presence of DDQ (2.0 equiv.) and $FeCl_3$ (0.2 equiv.) at room temperature, a polysubstituted naphthalene **6aa** was obtained in 68% yield instead of cyclopentene **3** (Scheme 2).

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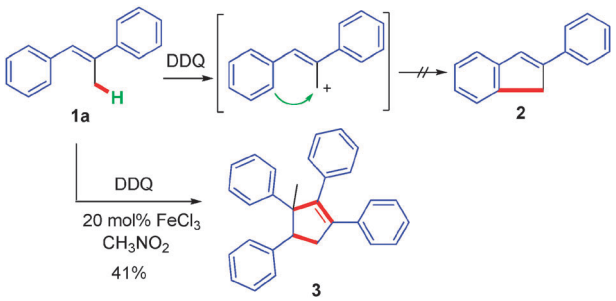
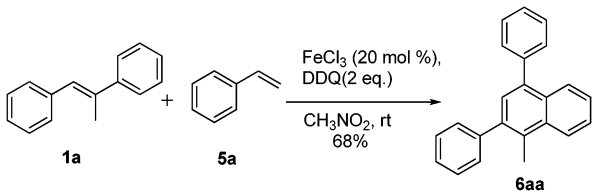
† Electronic supplementary information (ESI) available: General experimental procedure and the copies of ^1H and ^{13}C NMR for all new products. See DOI: 10.1039/c2cc17330a



Scheme 1 Model CDC reaction of **1a**.

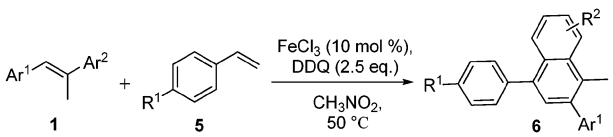


Scheme 2 The synthesis of naphthalene **6aa** *via* a tandem CDC.

To the best of our knowledge, this is the first example of tandem iron-catalyzed CDC[10] of monoactivated allylic sp^3 C–H with styrene to afford a polysubstituted naphthalene skeleton. Although, many efforts have been made to develop synthetic methods to access polysubstituted naphthalenes,[11] most synthetic methodologies involve rare/noble metal catalysts such as Au, Rh, Ru, Pd, *etc*. and prefunctional starting materials such as aryl halides, aryl boronates, aryl aldehyde, *etc*. Therefore, efficient and practical synthetic protocols are still urgently required to satisfy the increasing applications of naphthalenes in the synthesis of both biologically active compounds and π-conjugated functional materials.[12]

In order to understand the generality and scope of this remarkable process, a systematic screening of reaction conditions was performed which provided optimal reaction conditions as follows: substrate **1** (1 eq.)/styrene (2 eq.)/DDQ (2.5 eq.)/$FeCl_3$ (0.1 eq.)/CH_3NO_2/50 °C. Under these optimised reaction conditions, polysubstituted naphthalene **6aa** was obtained in 80% yield (see ESI†). Next, a series of substituted substrates were investigated (Table 1). It was found that substrates with strong electron-donating substituents on either Ar^1 or Ar^2 gave no product (entries 6 and 7), and other weakly electron-donating and electron-withdrawing substituents on either Ar^1 or Ar^2 gave moderate to good yields of the corresponding naphthalene (entries 2–5, 8 and 9). Moreover, substrates with different substituents on Ar^1 or Ar^2 gave exclusive regioselectivity of newly formed naphthalenes fused to the Ar^2 group to afford the corresponding products with the R^2 group mostly at position 6 of the naphthalene backbone (entries 2–4, 8 and 9). However, the reaction of **1e** with an electron-withdrawing bromo substituent at the *meta* position was relatively complicated and sluggish due to the *ortho*- and *para*-directing deactivating bromine, affording a 1 : 1 mixture of *ortho*- and *para*-product **6ea** and **6ea′** in 56% of overall yield (entry 5). Further investigation of substituent effects on both Ar^1 and Ar^2 furnished the corresponding products in similar yields to those of monosubstituted substrate **1** (entries 10–13). Interestingly, it was found that substrates **1f** and **1g** with a *para*-methoxy group on different aryl rings gave no desired product, the reasons for this observation remain unclear. However, substrate **1m**, bearing an electron-withdrawing bromo substituent on

Table 1 The synthesis of naphthalenes **6** *via* a tandem CDC process[a]



Entry	Ar^1/Ar^2	R^1	R^2	Yield[b] [%]
1	Ph, Ph (**1a**)	H (**5a**)	H	80
2	Ph, 4-MePh (**1b**)	H	6-Me	66
3	Ph, 4-ClPh (**1c**)	H	6-Cl	70
4	Ph, 4-BrPh (**1d**)	H	6-Br	61
5	Ph, 3-BrPh (**1e**)	H	7-Br/5-Br	56[c]
6	Ph, 4-OMePh (**1f**)	H	6-OMe	—[e]
7	4-OMePh, Ph (**1g**)	H	H	—[e]
8	4-MePh, Ph (**1h**)	H	H	70
9	4-BrPh, Ph (**1i**)	H	H	63
10	4-MePh, 4-BrPh (**1j**)	H	6-Br	67
11	4-BrPh, 4-MePh (**1k**)	H	6-Me	62
12	4-BrPh, 4-BrPh (**1l**)	H	6-Br	62[d]
13	4-BrPh,3-Br-4-OMePh (**1m**)	H	6-OMe-7-Br/6-OMe-5-Br	43[c]
14	Ph, Ph (**1a**)	4-OMe (**5b**)	H	—[e]
15	Ph, Ph (**1a**)	4-Me (**5c**)	H	33
16	Ph, Ph (**1a**)	4-Br (**5d**)	H	70
17	Ph, Ph (**1a**)	4-Cl (**5e**)	H	74
18	Ph, Ph (**1a**)	4-F (**5f**)	H	71
19	Ph, 2-naphthyl (**1n**)	H	—[f]	30

[a] Optimised reaction conditions were employed as follows: substrate **1** (0.3 mmol)/styrene (0.6 mmol)/DDQ (0.75 mmol)/$FeCl_3$ (0.03 mmol)/CH_3NO_2 (2 mL)/50 °C. [b] Isolated yield. [c] A mixture of regioisomers (1 : 1) was obtained. [d] The yield is calculated based on recovered starting material. [e] A mixture of unidentified products was observed. [f] An anthracene derivative, 1-methyl-2,4-diphenylanthracene, was obtained.

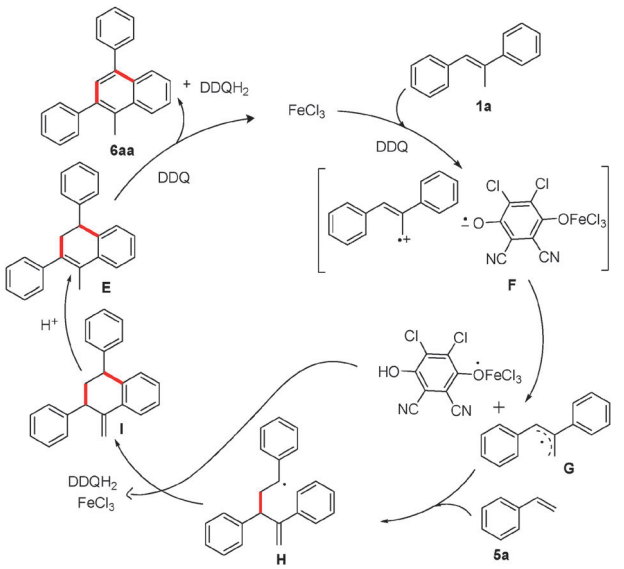


Fig. 2 Proposed reaction pathway for iron-catalysed tandem CDC.

each aryl ring, was found to give a mixture (1 : 1 ratio) of products **6ma** and **6ma′** in moderate yield (entry 13, 43% of overall yield).

Next, a series of styrenes with either electron-withdrawing or donating groups were investigated. Most styrenes afforded the corresponding polysubstituted naphthalenes in moderate to good yields (entries 15–18). Similar to methoxy containing substrates **1f–g**, styrene **5b** bearing an electron-donating methoxy group was also found to give no desired product (entry 14). Gratifyingly, when substrate **1n** was synthesised by replacing Ar^2 with a naphthyl motif, and employed for this novel CDC process, a trisubstituted anthracene derivative **6na** was obtained in 30% yield (entry 19).

In order to understand the mechanism, this model reaction was performed again with an additional 2.0 equiv. of TEMPO, and the formation of **6aa** was completely inhibited, which implies that a radical species may be involved in this reaction (Fig. 2).

In conclusion, we have demonstrated a novel iron-catalysed tandem cross-dehydrogenative coupling and benzoannulation process for the synthesis of biologically and synthetically important polysubstituted naphthalene derivatives from simple 1,2-aryl-propenes and styrenes in moderate to good yields. In this system, a highly controlled reaction regioselectivity was observed to give either cyclopentene or polysubstituted naphthalenes as a result of including or excluding styrene. Therefore, we believe that this new synthetic strategy will allow access to various functionalised naphthalenes, anthracenes and even more complicated aromatic ring systems, which would be of great benefit to synthesis and materials science. Further studies on the application of this protocol to the synthesis of more complicated aromatic ring systems and their physical properties are in the progress.

This work was supported by the Fundamental Research Funds for the Central Universities, the Natural Science Foundation of China (No. 21172068, 21050110426). We also thank Prof. Ning Jiao and Shuli You for helpful discussion.

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