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A Cu-Catalysed Radical Cross-Dehydrogenative Coupling Approach to Acridanes and Related Heterocycles

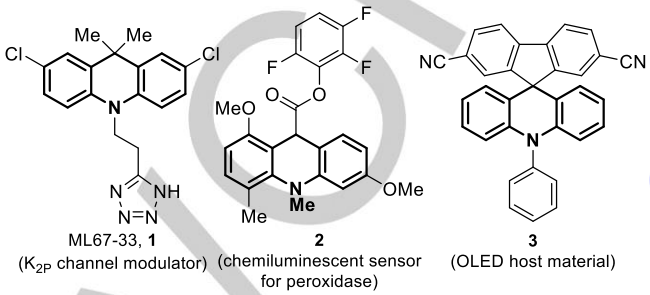
Timothy E. Hurst*[a] and Richard J. K. Taylor*[a]

Abstract: The synthesis of acridanes and related compounds via the Cu-catalysed radical cross-dehydrogenative coupling of simple 2-[2-(arylamino)aryl]malonates is reported. This method can be further streamlined to a one-pot protocol involving the *in situ* fomation of the 2-[2-(arylamino)aryl]malonate by α-arylation of diethyl malonate with a 2-bromodiarylamine under Pd-catalysis, followed by the subsequent Cu-catalysed cyclisation.

Introduction

In recent years C-H activation has emerged as a powerful and attractive method in organic synthesis since it enables the formation of C-C bonds without pre-functionalisation of one or both of the coupling partners, thus leading to more efficient and atom-economical processes. Within the wider pantheon of C-H activation, cross-dehydrogenative couplings (CDC) have proved to be versatile procedures for the selective formation of C-C bonds from two different C-H systems under oxidative conditions.[1] Our contribution in this area involves the synthesis of diverse nitrogen heterocycles via the Cu-catalysed oxidative coupling of C_{sp2}-H/C_{sp3}-H bonds;[2] a radical variant of the CDC processs.

9,10-Dihydroacridines (acridanes) have garnered much attention[3] due to their potent biological activity, including inhibition of class IIa histone deacetylase[4] and HIV reverse transcriptase,[5] neuroleptic activity,[6] and as activators of K_{2P} potassium channels[7] (*e.g.* **1**, Figure 1). Furthermore, acridanes have been employed as chemiluminescent sensors in immunoassays[8] (*e.g.* **2**), as NADH analogues in hydride-transfer reactions,[9] as host materials in OLEDs[10] (*e.g.* **3**), as photoswitches,[11] and as molecular motors.[12] Moreover, acridanes are valuable building blocks being readily oxidised to acridines and acridones,[13] functionalised by C-H activation,[14] and easily converted into 5*H*-dibenzo[*b*,*f*]azepines and 5,11-dihydro-10*H*-dibenzo[*b*,*e*][1,4]diazepines via ring expansion.[15]



ML67-33, **1** (K_{2P} channel modulator)

2 (chemiluminescent sensor for peroxidase)

3 (OLED host material)

Figure 1. Examples demonstrating the utility of acridanes.

Given the proven utility of acridanes, the sparse number of general methods available for their preparation is surprising.[3] Traditionally, they have been prepared by nucleophilic addition to existing acridines **4** or acridinium salts **5** (Scheme 1, eqn 1),[16] or by a Friedel-Crafts type cyclisation of diarylamines **7** with strong acid (Scheme 1, eqn 2).[17] However, the need to rely either on the commercial availability or potentially lengthy synthesis of acridines **4**, coupled with the requirements for the use of strong acids and well known problems of site-selectivity associated with Friedel-Crafts cyclisations, means that new approaches to highly substituted acridane derivatives are of considerable interest.

Thus, in continuation of our studies on the synthesis of diverse heterocyclic scaffolds via the oxidative cyclisation of linear precursors using inexpensive copper salts,[2] our goal was to exploit this simple yet powerful methodology in the preparation of acridane derivatives **10** from 2-[2-(arylamino)aryl]malonates **9** (Scheme 1, eqn 3).

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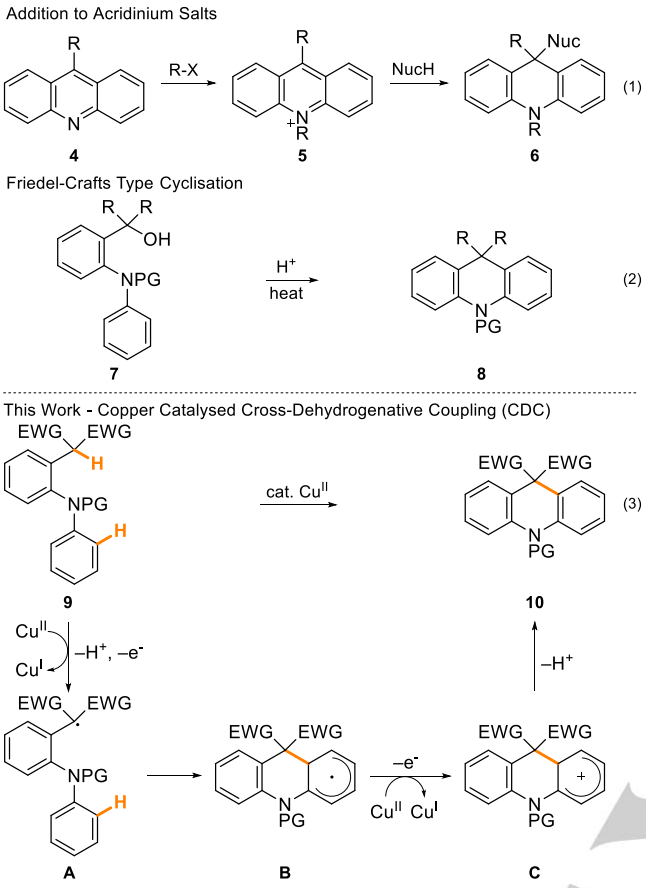


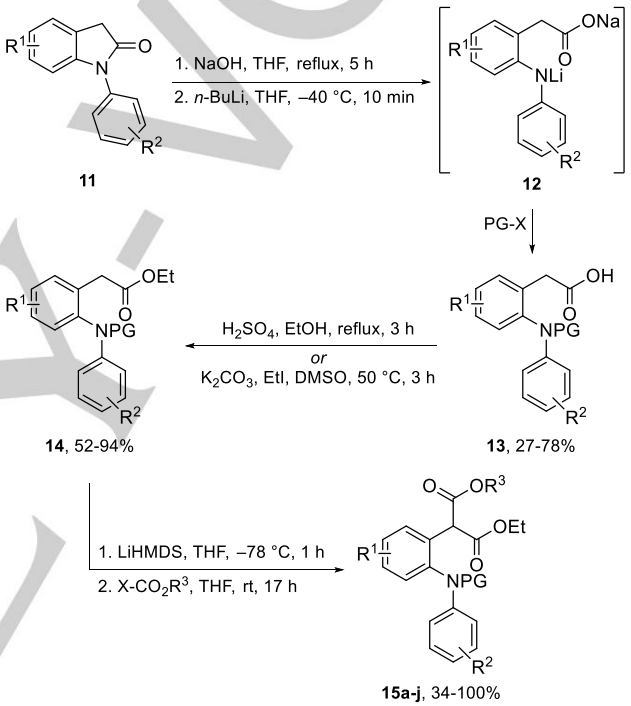
Scheme 1. Approaches for the synthesis of acridanes.

The likely mechanism for this process, by analogy with earlier studies,[2d,2f] is shown in Scheme 1. Initially, proton abstraction and single electron oxidation would give malonyl radical **A**, which would undergo intramolecular homolytic aromatic substitution to give **B**, followed by further oxidation to give the cyclohexadienyl cation **C**, which would finally aromatise to generate the desired product **10**. Evidence for a radical based mechanism in these copper-mediated oxidative coupling reactions includes radical clock experiments,[2d] as well as DFT calculations conducted by Kündig in related systems.[2f] Clearly, two equivalents of copper salt are nominally required to effect both single electron oxidations involved in the process. However, in related studies we have demonstrated that a catalytic amount of the copper salt may be used with air serving as the terminal oxidant.[2a-d]

Results and Discussion

The initial task was to develop a flexible and modular approach for the synthesis of linear precursors **15** (Scheme 2) which would allow the facile introduction of substituents at various positions around the acridane skeleton.

In the event, *N*-aryloxindoles **11** proved to be versatile starting materials for the preparation of cyclisation precursors **15** via a 3 step protocol (Scheme 2). First, ring-opening of the lactam moiety was carried out by treatment with NaOH in refluxing THF, followed by *in situ* formation of the dianions **12** by addition of *n*-BuLi at low temperature and subsequent trapping with the appropriate electrophile to give carboxylic acids **13**.[18] Then, simple esterification, deprotonation with LiHMDS and trapping with the requisite cyano- or chloroformate delivered 2-[2-(arylamino)aryl]malonates **15a-j**. In this manner, control over the substitution pattern on the aromatic rings, as well at the nitrogen atom and ester functionality could be readily achieved (14–63% unoptimised overall yields; see SI for details).



Scheme 2. Modular synthesis of cyclisation precursors **15a-j**.

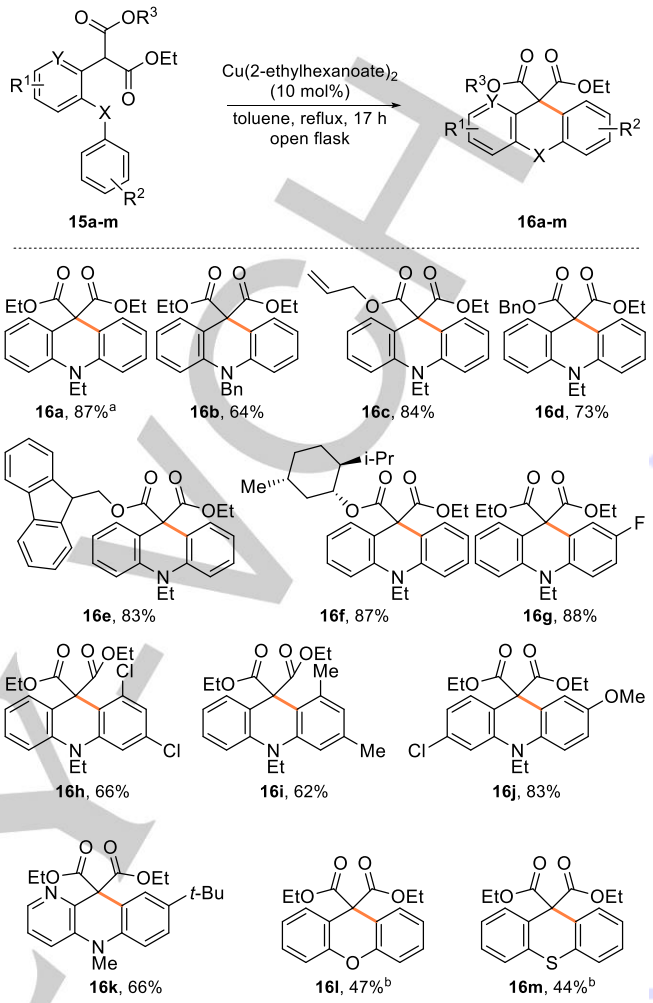
With ready access to the required linear substrates established, the cyclisation of model substrate **15a** was then examined. Pleasingly, treatment of **15a** under the conditions previously reported[2b] in our synthesis of oxindoles [Cu(2-ethylhexanoate)$_2$ (10 mol%), toluene, reflux, open flask] delivered the desired acridane **16a** in 87% yield without the need for further optimisation (Scheme 3). It is also noteworthy that the oxidative coupling could be performed in the presence of only 5 mol% or 2 mol% of the catalyst, with only a minor drop in yield (Scheme 3, footnote a).

Following this successful initial result, the generality of this new copper-catalysed approach to acridanes was explored (Scheme 3). First, cyclisation of **15b**, bearing a removable protecting group on nitrogen, was carried out to give *N*-benzylacridane **16b**, albeit in reduced yield compared to *N*-ethyl derivative **16a**. Next, acridanes **16c-f** bearing differentially

protected esters (*e.g.* allyl, Bn, Fmoc) were prepared, thus opening the possibility for further manipulation of the cyclised products (*vide infra*). The Fmoc-protected ester **16e** was crystalline, allowing unambiguous confirmation of its structure through X-ray crystallographic analysis (see SI).

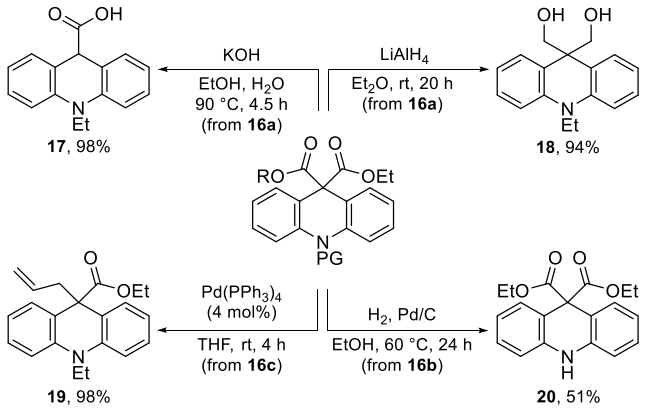
Next, the introduction of substituents at various positions on either aromatic ring of the acridane skeleton was explored, with **16g-j** obtained in good to excellent yields. Incorporation of a nitrogen atom into one of the aromatic rings was also possible, leading to isolation of the corresponding aza-acridane **16k** in 66% yield.

Having established the effectiveness of the copper-catalysed route to acridanes **16a**-**k**, this method was extended to the synthesis of other related heterocycles of interest, such as xanthenes and thioxanthenes (Scheme 3, last two entries). However, cyclisation of a linear diaryl ether in the presence of 10 mol% Cu(2-ethylhexanoate)$_2$ under the standard reaction conditions delivered xanthene **16l** in a disappointing 33% yield. Also isolated was an equal amount of a by-product identified as ethyl 2-oxo-2-(2-phenoxyphenyl)acetate, which arises from competing decarboxylation and aerial oxidation of the starting material. This problem was exacerbated in the case of thioxanthene **16m**, which was isolated in only 20% yield along with 53% of the undesired by-product. Further optimisation of these latter processes is clearly required but fortunately, in both cases, the yield of the oxidation by-products could be minimised by performing the cyclisation under an atmosphere of argon, leading to formation of xanthene **16l** and thioxanthene **16m** in 47% and 44% yields, respectively. While formation of the desired products **16l** and **16m** is enhanced under these conditions, performing the reaction under argon necessitates the use of 2.5 equivalents of copper salt to allow the reaction to proceed to completion (see proposed mechanism, Scheme 1)



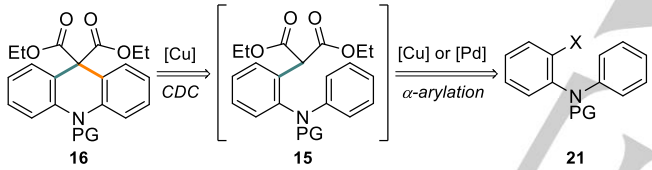
Scheme 3. Scope of the Cu-catalysed synthesis of acridanes. [a] **16a** was obtained in 83% and 84% yield when Cu(2-ethylhexanoate)$_2$ (5 mol% and 2 mol%) were used, respectively. [b] Cu(2-ethylhexanoate)$_2$ (2.5 equiv) and DIPEA (2.5 equiv) were used under an atmosphere of argon.

In order to demonstrate the utility of the acridanes derived from the copper-catalysed cyclisation, a brief study on their further functionalisation was carried out (Scheme 4). For example, treatment of **16a** with an excess of KOH in EtOH/H_2O resulted in saponification and decarboxylation to give acid **17** in excellent yield, thus providing an alternative route which may be of use in the synthesis of analogues of chemiluminescent sensors such as **2** (Figure 1). Reduction of the esters was also achieved in the presence of $LiAlH_4$ to give diol **18** in 94% yield. Furthermore, selective functionalisation of the allyl ester in **16c** was carried out by decarboxylative allylic alkylation on treatment with 4 mol% $Pd(PPh_3)_4$ to give **19**, thereby generating a new quaternary carbon centre, again in excellent yield. Finally, hydrogenolysis of the benzyl protecting group in **16b** delivered acridane **20** bearing a free N-H group in reasonable, un-optimised yield.



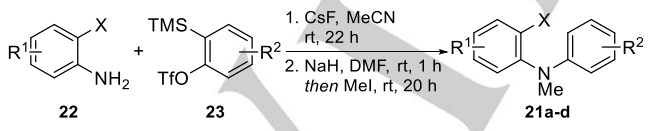
Scheme 4. Further derivatisation of acridanes obtained from oxidative coupling.

In a final aspect to this work, we explored the potential of an expedited, one-pot approach to acridanes **16** based on the α-arylation of 1,3-dicarbonyl compounds with haloarenes **21** generating intermediates **15** *in situ* which would then undergo the oxidative coupling procedure (Scheme 5). Given the well-known ability of copper salts to catalyse both processes,[19] a highly efficient transformation seemed attainable.



Scheme 5. Retrosynthesis of acridanes **16** *via* a one-pot α-arylation/cyclisation process.

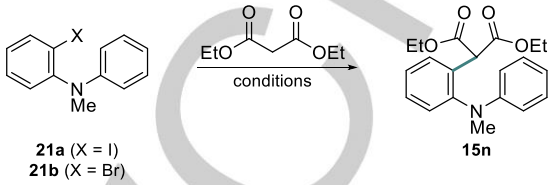
The requisite 2-halodiarylamines **21** were easily prepared by the addition of commercially available 2-haloanilines **22** to benzynes prepared *in situ* from 2-(trimethylsilyl)phenyl triflates **23** in the presence of CsF, then subsequent *N*-alkylation (Scheme 6; see SI for more details).[20]



Scheme 6. Synthesis of 2-halodiarylamines **21a**-**d**.

Next, the crucial transition-metal catalysed α-arylation reaction between diethyl malonate and 2-halodiarylamines **21a**-**b** was examined, selected results of which are shown in Table 1. In the event, none of the desired α-arylation product was observed on heating either 2-iodo- or 2-bromo-*N*-methyl-*N*-phenylaniline **21a**-**b** with diethyl malonate in the presence of CuI and 2-picolinic acid[19a] (Table 1, entries 1-2). Similarly, other copper-based catalyst systems reported[19b-d] for the coupling of dialkyl malonates with simple haloarenes proved equally ineffective (results not shown). Thus, attention turned to the use of palladium catalysts to effect the initial transformation.

Table 1. Optimisation of the α-arylation of **21a**-**b** with diethyl malonate.



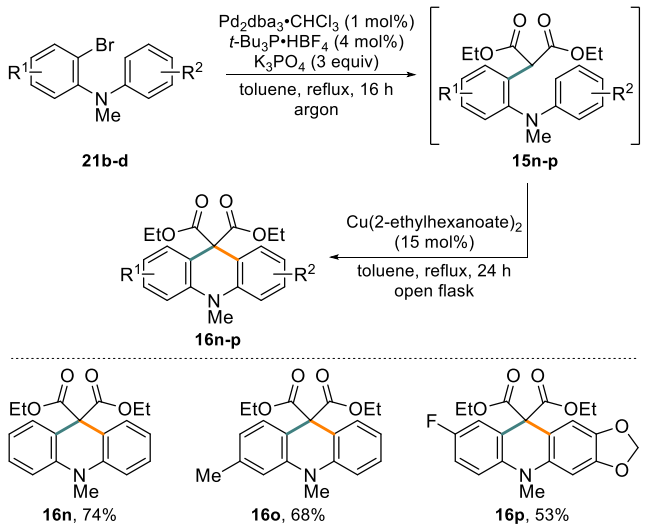
Entry	X	Conditions	Yield
1	I	CuI (10 mol%), 2-picolinic acid (20 mol%) Cs_2CO_3 (3 equiv), dioxane, reflux, 17 h	–[a]
2	Br	CuI (10 mol%), 2-picolinic acid (20 mol%) Cs_2CO_3 (3 equiv), dioxane, reflux, 17 h	–[a]
3	I	$Pd(OAc)_2$ (2 mol%), ^{t}BuMePhos (4.4 mol%) K_3PO_4 (2.4 equiv), toluene, reflux, 18 h	–[a]
4	Br	$Pd(OAc)_2$ (2 mol%), ^{t}BuMePhos (4.4 mol%) K_3PO_4 (2.4 equiv), toluene, reflux, 18 h	–[a]
5	I	$Pd_2dba_3{\cdot}CHCl_3$ (1 mol%), ^{t}Bu$_3$P·HBF$_4$ (4 mol%) K_3PO_4 (3 equiv), toluene, 70 °C, 15 h	32%
6	I	$Pd_2dba_3{\cdot}CHCl_3$ (1 mol%), ^{t}Bu$_3$P·HBF$_4$ (4 mol%) K_3PO_4 (3 equiv), toluene, reflux, 14 h	61%
7	**Br**	**$Pd_2dba_3{\cdot}CHCl_3$ (1 mol%), ^{t}Bu$_3$P·HBF$_4$ (4 mol%) K_3PO_4 (3 equiv), toluene, reflux, 17 h**	**72%**

[a] Starting materials only were observed by ^{1}H NMR analysis of the unpurified reaction mixture.

No α-arylation was observed using the $Pd(OAc)_2$/*t*-BuMePhos catalyst system developed by Buchwald (Table 1, entries 3-4),[21] but an encouraging 32% yield of **15n** was obtained on switching to $Pd_2dba_3{\cdot}CHCl_3$ (1 mol%) as the catalyst with the bench stable ligand ^{t}Bu$_3$P·HBF$_4$ (4 mol%) in toluene at 70 °C (Table 1, entry 5).[22] Increasing the reaction temperature allowed us to isolate 2-[2-(arylamino)aryl]malonate **15n** in 61% (from **21a**) and 72% (from **21b**) yields, respectively.

With conditions for the malonate coupling in hand, attention then turned to establishing the one-pot α-arylation/cyclisation protocol to prepare acridanes directly (Scheme 7). To this end, the Pd-catalysed α-arylation reaction between 2-bromo-*N*-methyl-*N*-phenylaniline **21b** and diethyl malonate was first carried out using the optimised conditions described above under an atmosphere of argon. Subsequently, the reaction flask was simply opened to the air, Cu(2-ethylhexanoate)$_2$ (15 mol%) was added, and heating continued for a further 24 h to facilitate the cyclisation. In this manner, the target acridane **16n** was isolated in a pleasing 74% overall yield over the 2 steps. Furthermore, substituents could be readily introduced on one, or both, aromatic rings, allowing access to more highly substituted

acridanes such as **16o** and **16p** using this efficient one-pot procedure.



Scheme 7. Scope of the one-pot α-arylation/cyclisation approach to acridanes.

Conclusions

In summary, we report a Cu-catalysed radical cross-dehydrogenative coupling approach to acridanes and related heterocycles from readily available 2-[2-(arylamino)aryl]malonates. This highly atom-economical method uses inexpensive Cu(2-ethylhexanoate)$_2$ as the catalyst under mild conditions, thus avoiding many of the problems associated with existing classical strategies for the synthesis of acridanes. The diester moiety resulting from the oxidative coupling reaction serves as a useful handle for further functionalisation. In addition, we have established a streamlined protocol involving the *in situ* formation of the cyclisation precursor by the α-arylation of diethyl malonate with a 2-bromodiarylamine under Pd-catalysis, followed by subsequent Cu-catalysed cyclisation to give the acridanes in a single pot. Further studies will be carried out to utilise this new methodology in target synthesis.

Experimental Section

Representative procedure for the copper-catalysed synthesis of acridanes: To a solution of the cyclisation precursor **15** (1.00 mmol) in toluene (10 mL) was added copper(II) 2-ethylhexanoate (35.0 mg, 0.100 mmol). The reaction mixture was heated at reflux (oil bath at 120 °C) for 17 h with the condenser left open to the air. After cooling to rt, saturated NH_4Cl (25 mL) was added and the aqueous phase extracted with EtOAc (3 × 25 mL). The combined organics were washed with 10% NH_4OH (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexane, afforded the title compound **16** (see SI for details).

Acknowledgements

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Keywords: acridanes • copper • catalysis • cross-dehydrogenative coupling • one-pot

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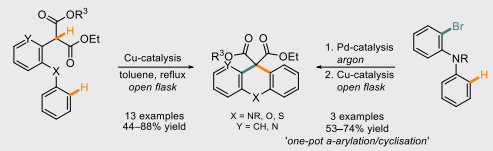

Copper Catalysis

Timothy E. Hurst and Richard J. K. Taylor**

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A Cu-Catalysed Radical Cross-Dehydrogenative Coupling Approach to Acridanes and Related Heterocycles

The synthesis of acridanes and related compounds via the Cu-catalysed oxidative cyclisation of simple linear precursors is described. A one-pot protocol involving α-arylation of diethyl malonate with a 2-bromodiarylamine under Pd-catalysis, followed by the subsequent Cu-catalysed cyclisation is also demonstrated.