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Versatile ruthenium(II)-catalyzed C–H cyanations of benzamides†

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Direct cyanations of arenes and heteroarenes bearing only weakly coordinating amides were accomplished using a robust ruthenium(II) catalyst. The user-friendly C(sp²)–H activation occurred with the assistance of carboxylate with high site-selectivity, excellent functional group tolerance and ample scope.
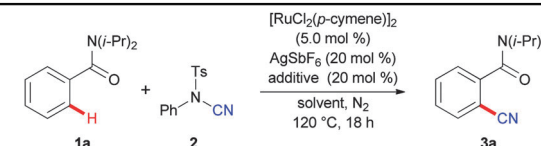
Aromatic nitriles constitute key structural motifs of important pharmaceuticals, dyes, agrochemicals and natural products.[1–3] The cyano group serves as a versatile functional group that can easily be transformed into amines, ketones or aldehydes, among others.[4] The syntheses of aryl nitriles continue to rely on classical approaches, such as the Sandmeyer[5] or the Rosenmund–von Braun reaction,[6,7] which have severe limitations, including the use of stoichiometric or even super-stoichiometric amounts of metal cyanides as well as harsh reaction conditions. An alternative approach is represented by transition metal-catalyzed cyanations of aryl halides or boronic acids under milder reaction conditions.[8] These catalyzed coupling reactions thereby also display a considerably improved functional group tolerance. However, this strategy exploits prefunctionalized substrates, the preparation of which requires numerous functional group interconversions and generates undesired waste.

The catalytic activation of otherwise inert C(sp²)–H bonds as latent functional groups has in recent years emerged as an increasingly viable tool for improving the atom- and step-economy of organic synthesis.[9] Thus, Yu developed direct cyanations of 2-arylpyridines.[10,11] The research groups of Jiao[12] and Chang[13] reported on oxidative cyanations of electron-rich substrates with nonmetallic cyano-group sources in the presence of stoichiometric sacrificial oxidants,[14,15] while Hartwig disclosed a two-step iridium-catalyzed borylation/copper-mediated cyanation protocol.[16] Very recently, rhodium-catalyzed C–H cyanations of arenes were accomplished, albeit exploiting rather strongly coordinating directing groups, such

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as oxazolines, oximes, pyrazoles or pyridines.[17–19] Herein, we wish to disclose an alternative strategy, which involves the use of relatively inexpensive[20] ruthenium(II) catalysts[21] for the first time for C(sp²)–H cyanations. Importantly, the versatile ruthenium catalyst enabled expedient C–H cyanations with easily accessible *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS, **2**) as the most user-friendly cyanation reagent for the functionalization of only weakly coordinating[22] aromatic and heteroaromatic amides – key structural scaffolds in organic synthesis and medicinal chemistry.

We initiated our studies by probing the effect of different additives and solvents on the envisioned C–H bond cyanation using synthetically useful benzamide **1a** (Table 1).

Thus, [RuCl₂(*p*-cymene)]₂ enabled the desired direct cyanation when using both AgSbF₆ and AgOAc as additives in DCE as the

Table 1 Optimization of C–H cyanation with benzamide **1a**[a]

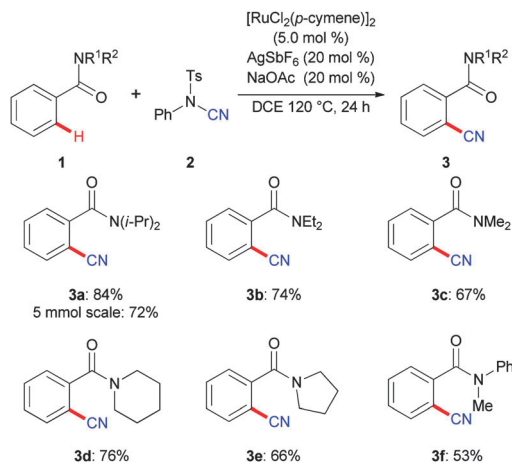| Entry	Additive	Solvent	Yield (%)
1	AgOAc	DCE	77 (70)
2	Cu(OAc)₂	DCE	30
3[b]	AgOAc	DCE	80 (67)
4[c]	AgOAc	DCE	<5
5[d]	AgOAc	DCE	67 (54)
6	AgOAc	1,4-Dioxane	38
7	AgOAc	*o*-Xylene	21
8	AgOAc	Toluene	23
9	AgOAc	DMF	<2
10[e]	AgOAc	DCE	<2
11	KOAc	DCE	<5
12	CsOAc	DCE	17
13	**NaOAc**	**DCE**	**90 (80)**
14[f]	**NaOAc**	**DCE**	**95 (84)**

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), [RuCl₂(*p*-cymene)]₂ (5.0 mol%), AgSbF₆ (20 mol%), additive (20 mol%), solvent (2.0 mL), 120 °C, 18 h; GC-conversion, isolated yields are given in parentheses. [b] AgOAc (30 mol%). [c] Without AgSbF₆. [d] AgSbF₆ (30 mol%). [e] Without [RuCl₂(*p*-cymene)]₂. [f] 24 h.

Scheme 1   Effect of *N*-substituents on C–H cyanations.

solvent (entries 1–5). DCE proved to be the solvent of choice (entries 1 and 6–9), while a test reaction illustrated that the C–H bond activation did not occur in the absence of the ruthenium catalyst (entry 10). Among a set of representative metal acetate additives,[23,24] NaOAc furnished the highest yields of the product **3a** (entries 11–14).

With the optimized catalytic system in hand, we explored the effect exerted by the *N*-substituent at the amide moiety (Scheme 1). A variety of tertiary amides **1a–1f** proved to be suitable substrates with optimal results being accomplished with the sterically hindered substrate **1a**.[25] A comparable catalytic efficacy was obtained when performing the C–H bond cyanation on a larger 5 mmol scale.

Subsequently, we tested the scope of the catalytic system for the cyanation of aromatic amides **1** (Scheme 2). The robust ruthenium(II) complex proved to be highly chemo-selective. Thus, the catalyst tolerated a set of valuable electrophilic functional groups, such as ester, fluoro, chloro, bromo and even iodo groups, which should be invaluable for the further diversification of the thus obtained products **3**.
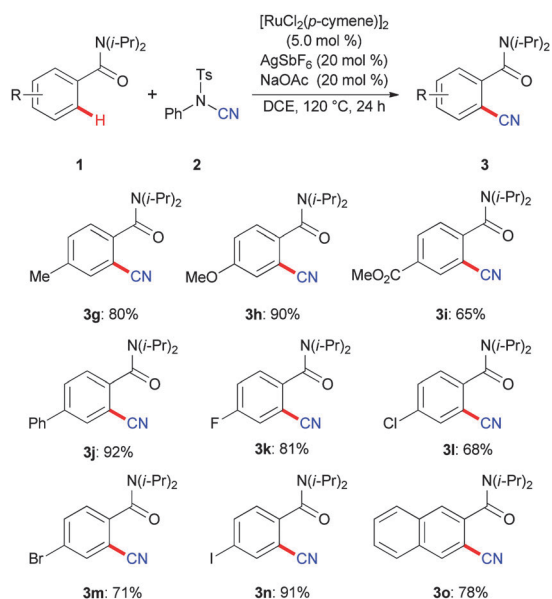
Scheme 2   Scope of ruthenium-catalyzed C–H cyanation with amides **1**.
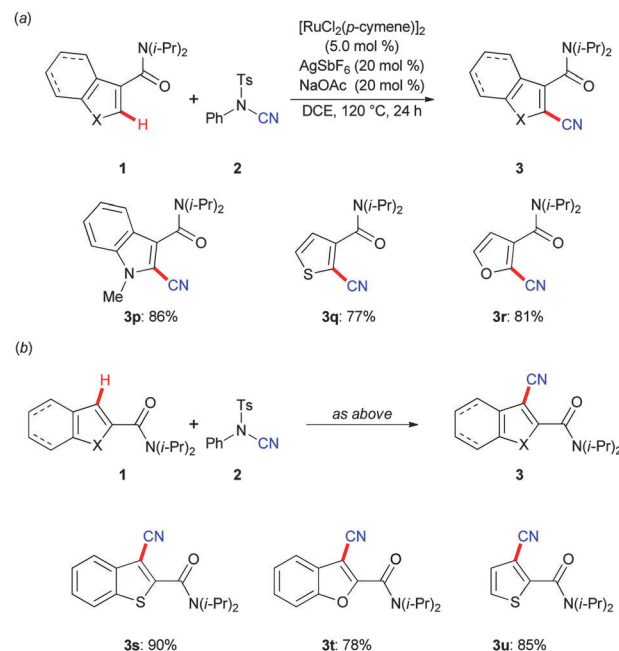
Scheme 3   C–H cyanation with heteroaromatic amides **1**.

The user-friendly ruthenium(II) catalyst was not limited to the functionalization of arenes. Indeed, challenging heteroaromatic substrates **1p–1u** were efficiently directly functionalized both at positions C–2 (Scheme 3a) as well as C–3 (Scheme 3b). Thereby, cyanated thiophenes, furanes, benzothiophenes, benzofuranes and indoles were obtained in a chemo- and site-selective fashion.

The well-defined ruthenium(II) biscarboxylate complex **4**[26] displayed a catalytic activity comparable to the one observed when using the *in situ* generated system, notably even in the absence of NaOAc (Scheme 4).

In consideration of the unique chemo-selectivity and outstanding efficacy of our ruthenium catalyst, we became interested in delineating its mode of action. To this end, intramolecular competition experiments with *meta*-substituted substrates **1v–1x** revealed a considerable secondary directing group effect[27] exerted by a methoxy substituent and, even more pronounced, by a fluoro group present in benzamides **1w** and **1x**, respectively (Scheme 5).
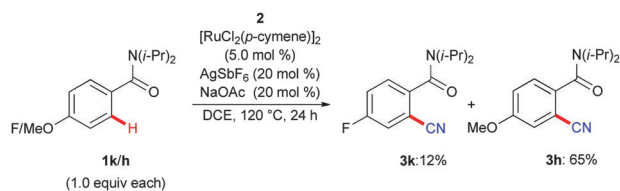
Intermolecular competition experiments between differently decorated amides indicated electron-rich arenes to be preferentially converted (Scheme 6), which can be rationalized in terms of an electrophilic-type activation mode of the cationic ruthenium species.

In support of this hypothesis, we observed a rather low kinetic isotope effect (KIE) of $k_H/k_D \approx 1.2$ (see the ESI†). Moreover, C–H bond activation conducted in the presence of D_2O as the cosolvent
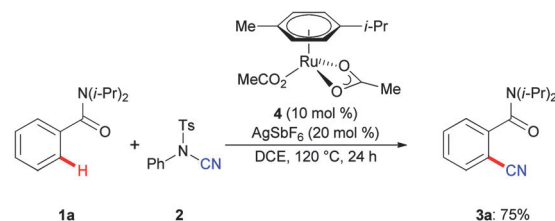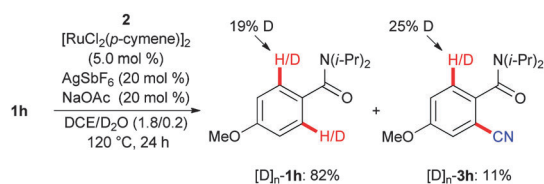

Scheme 4   Well-defined complex **4** as the catalyst.
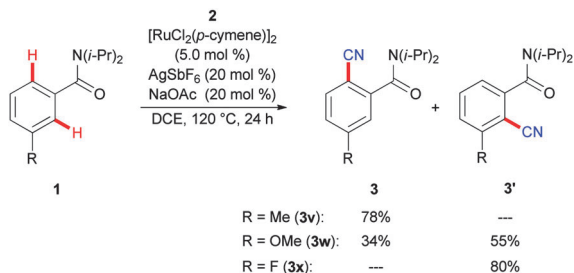
Scheme 5 Intramolecular competition experiments with *meta*-substituted arenes **1**.


Scheme 6 Intermolecular competition experiments with arenes **1**.

Scheme 7 H/D exchange reaction.

revealed a reversible H/D-exchange reaction, as was observed for the reisolated starting material [D]$_n$-**1h** as well as the product [D]$_n$-**3h** (Scheme 7).

Based on these mechanistic studies we propose a plausible catalytic cycle to initiate a reversible C–H bond metalation on amides **1**[28] to furnish cationic complex **6** (Scheme 8). Thereafter, coordination and
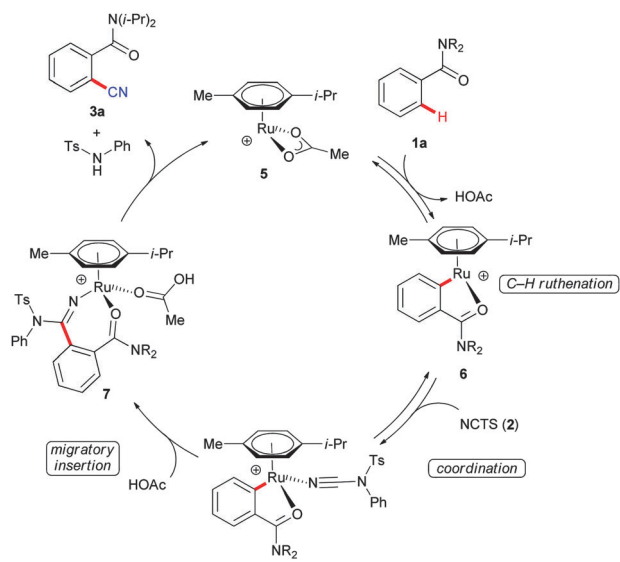
Scheme 8 Plausible catalytic cycle.

insertion of NCTS (**2**) give rise to key intermediate **7**. Subsequently, β-elimination provides the desired product **3**, while proto-demetalation regenerates the cationic ruthenium(II) carboxylate catalyst **5**.

In summary, we have reported on the use of relatively inexpensive ruthenium-catalyzed C(sp^2)–H bond cyanation on arenes for the first time. The robust direct cyanation[29,30] occurred site-selectively on synthetically useful aromatic and heteroaromatic amides with ample scope. Experimental mechanistic studies provided strong support for a reversible C–H metalation mechanism by a cationic ruthenium(II) complex.

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