Dual Ligand-Enabled Nondirected C–H Cyanation of Arenes

Hao Chen, Arup Mondal, Manuel van Gemmeren

Abstract: Aromatic nitriles are key structural units in organic chemistry and thus highly attractive targets for C–H activation. Herein the development of an arene-limited, nondirected C–H cyanation based on the use of two complementary ligands is reported. The reaction enables the cyanation of arenes by C–H activation in the absence of directing groups and is thus complementary to established approaches.

Aromatic nitriles are highly useful synthetic intermediates as well as important motifs in natural products and pharmacologically active compounds. Thus, it is not surprising that a variety of approaches have been pursued for their synthesis.[1] Besides traditional functional group interconversions, such as benzamide to benzonitrile dehydrations, methods starting from non-functionalized arenes and building upon a C–H functionalization or activation are particularly attractive, due to their potential to introduce molecular complexity and utilize more easily available starting materials. Several approaches towards this goal are depicted in Scheme 1A. Firstly, it is not surprising that established methods for the introduction of other functional groups, such as boronic esters or halides, can be combined with the conversion of the respective functionality into a nitrile, e.g. by the Rosenmund-von Braun reaction in the case of aryl bromides (Approach 1).[2] While this approach is suited to deliver a variety of aromatic nitriles, it faces the inherent disadvantage of requiring several steps and relying on another C–H functionalization as a source of the required reactivity and selectivity.[3] Alternatively, arene C–H cyanations via radical pathways have been developed which, given that the substrate is suitably substituted to stabilize the radical intermediate, can deliver the desired benzonitrile derivatives (Approach 2).[4] While this approach can be highly efficient, the reactivity and selectivity of these reactions are dictated by radical stability. Thus, a complementary method based on a C–H activation remains highly desirable. However, to date methods based on a C–H activation have remained limited to substrates bearing suitable directing groups (DGs) to enable the desired reactivity (Approach 3).[5,8]

We have recently developed a novel strategy for the Pd-catalyzed nondirected activation of aromatic C-H bonds that is based on the use of two complementary ligands and have applied it to the arene limited nondirected olefination of arenes (Scheme 1B).[7] Herein we report the development of an arene limited nondirected C–H cyanation of arenes based on this dual ligand approach.[8]

Scheme 1. Established approaches for the C–H cyanation of arenes (A) and our proof or concept for the dual ligand-enabled nondirected C–H activation of arenes (B).

Starting from the conditions reported in our study on the olefination of arenes, we could, through the introduction of suitable cyanide sources and an extensive optimization of the reaction conditions, develop two complementary sets of reaction conditions using copper(I) cyanide and zinc cyanide respectively. The results obtained under these conditions, as well as control experiments confirming the necessity for both ligands are shown in Table 1.

[*] Hao Chen, Arup Mondal, Dr. M. van Gemmeren
Max Planck Institute for Chemical Energy Conversion
Stiftstrasse 34-36, 45470 Mülheim an der Ruhr (Germany)
Dr. M. van Gemmeren
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstraße 40, 48149 Münster (Germany)
E-mail: mvangemmeren@uni-muenster.de

Supporting information for this article is given via a link at the end of the document.
The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

The first set of reaction conditions was identified using toluene (1a) as model compound. Using copper(I) cyanide as the cyanide source with silver fluoride as oxidant the reaction (%), CuCN (2 equiv), 1,1,1,3,3,3-hexafluoroiso-propanol (HFIP, 1 mL), 80 °C, 18 h. [b] GC analysis using 1,3,5-trimethoxybenzene as an internal standard.
and was formed as a mixture of ortho and para regioisomers, thus highlighting the influence of electronic effects on the regioselectivity of the reported method. As expected due to the analogy with our previous study on the olefination of arenes,[7] a chloro substituent had an ortho-directing effect and the product 2k derived of chlorobenzene was obtained in an o:p:m-ratio of 46:22:32. In light of the particular attractiveness of arene-centered methodologies for the functionalization of multiply substituted starting materials, we proceeded to evaluate the performance of our method with di- and tri-substituted substrates. Both meta- and ortho-xylene were suitable substrates giving the products 2i and 2m respectively. The observation that 2i was obtained as a 79:21 ratio of regioisomers, while 2m was formed as a single isomer can be rationalized by the competition between electronic and steric effects in the former case, while these effects work in the same direction in the latter case. We next explored fused bicyclic-substrates, leading to the formation of products 2n–q. The products 2n and 2o derived of indane and tetraline respectively were both obtained in good yields and with regioselectivities in favor of the less hindered position, albeit with a lower selectivity than for 2m, which reflects the reduction of steric demand in these substrates. Isochromane and protected tetrahydroisoquinoline could both be converted, giving 2p and 2q in moderate yield. Di-substituted substrates bearing halide substituents were also found to be tolerated, giving access to the products 2r and 2s with a chloride and fluoride substituent respectively. Finally, the tri-substituted products 2t–x bearing alkyl, halide, and methoxy substituents were all obtained in good yields and with regioselectivities that are in good agreement with the previously observed trends. Overall, the studies on the scope of the developed protocol show its applicability to a wide range of substitution patterns as well as a functional group tolerance ranging from a strongly electron-donating methoxy group to moderately electron-withdrawing halide substituents.

In summary, we have developed the first example of an arene-limited non directed cyanation of arenes through a C–H activation. The method is based on the use of a Pd(II) catalyst with two complementary ligands, both of which were shown to be essential for the success of the reaction. The protocol described is applicable to a broad range of substitution patterns and proceeds under a combination of electronic and steric control. The possibility to cyanate substrates bearing electron-donating as well as moderately electron-withdrawing substituents, both of which can be used as the limiting reagents, is expected to render this method attractive in the context of late stage modification. Further studies on the application of dual-ligand enabled nondirected C–H activations as well as regarding the mechanistic details underlying these processes are currently ongoing in our laboratories.

Experimental Section

General procedure A: An oven dried 10 mL Schlenk tube was charged with Pd(OAc)₂ (4.5 mg, 0.020 mmol, 10 mol %), L₁ (7.9 mg, 0.040 mmol, 20 mol %), N-acetyl-glycine (7.0 mg, 0.060 mmol, 30 mol %), AgF (101.5 mg, 0.8000 mmol, 4 equiv), arene (0.200 mmol), CuCN (35.8 mg, 0.400 mmol, 2 equiv), and HFIP (2 mL) under argon atmosphere. The reaction vessel was tightly sealed and placed into the outside circle of an aluminum block with a tightly fitting recess on a magnetic stirrer. The reaction mixture was stirred at room temperature for 2 minutes. The aluminum block was heated to 90 °C and the reaction mixture was stirred with 1000 rpm at this temperature for 18 h. The reaction mixture was allowed to cool to room temperature, transferred into 100 mL round-bottom flask, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using a gradient of pentane:ethyl acetate = 500:1 to 1:1 as the eluent.

General procedure B: An oven dried 10 mL Schlenk tube was charged with Pd(OAc)₂ (4.5 mg, 0.020 mmol, 10 mol %), L₁ (7.9 mg, 0.040 mmol, 20 mol %), N-acetyl-glycine (7.0 mg, 0.060 mmol, 30 mol %), AgF (76.0 mg, 0.600 mmol, 3 equiv), arene (0.200 mmol, 1 equiv), Zn(NC)₂ (47.0 mg, 0.400 mmol, 2 equiv), and HFIP (2 mL) under argon atmosphere. The reaction vessel was tightly sealed and placed into the outside circle of an aluminum block with a tightly fitting recess on a magnetic stirrer. The reaction mixture was stirred at room temperature for 2 minutes. The aluminum block was heated to 80 °C and the reaction mixture was stirred with 500 rpm at this temperature for 18 h. The reaction mixture was allowed to cool to room temperature, transferred into 100 mL round-bottom flask, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using a gradient of pentane:ethyl acetate = 500:1 to 1:1 as the eluent.

Acknowledgements

We gratefully acknowledge financial support from the Max Planck Society (Otto Hahn Award to M.v.G.), FCI (Liebig Fellowship to M.v.G.), and WWU Münster. We thank the members of our NMR and MS departments for their excellent service. Furthermore, we are indebted to Prof. F. Glorius for his generous support. We thank Philipp Wedi, Sabine Bognar, and Kiron Kumar Ghosh for proof reading this manuscript.

Keywords: C–H activation • Cyanation • Dual-ligand catalysis • Palladium • Nitriles

During the preparation of this manuscript we became aware of a parallel study by the Yu-group, which is currently available on the ChemRxiv preprint server: 10.26434/chemrxiv.7069658.v1
