Chinese Journal of Catalysis 39 (2018) 1782–1791

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Article

Chemo-selective couplings of anilines and acroleins/enones under substrate control and condition control

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ARTICLE INFO

Article history:
Received 29 June 2018
Accepted 5 July 2018
Published 5 November 2018

Keywords:
Rh(III)-catalysis
Chemo-selectivity
Annulation
Substrate control
Condition control

ABSTRACT

Rh(III)-catalyzed C–H activation of *N*-protected anilines and chemo-divergent couplings with acroleins/enones have been realized for synthesis of three classes of heterocycles. The oxidative coupling of *N*-pyridylaniline afforded dihydroquinolones with the acrolein being a major hydrogen acceptor. When the directing group was replaced by pyrimidyl in the same system, redox-neutral coupling occurred to afford hemiaminal ethers. Oxidative annulation of *N*-pyridylanilines with enones using $AgBF_4$ oxidant afforded atropisomeric quinolinium salts.

1. Introduction

Metal-catalyzed activation of C–H bonds has allowed development of numerous efficient approaches to access various value-added organics, especially heterocycles [1–11]. In C–H activation chemistry, chemo-, regio-, or stereoselectivity of C–H activation constitutes a central challenge in that environmentally analogous C–H bonds are generally present. Consequently, controlling selectivity of C–H activation has received increasing attention [12–18]. Despite the significant progress, regulation of redox-selectivity has been less studied [19–21].

Organic redox reactions, classically defined as gaining/losing hydrogen/oxygen, are ubiquitous. The transfer of a hydrogen atom in the form of a hydride, radical, or proton contributes to redox-diversity [22–25]. For example, elimination of a hydride from organics leads to oxidation, while proton transfer retains the oxidation state. Regulating the redox-chemistry of catalytic reactions represents an important task, and ideally all the three oxidation states (oxidation, reduction, and redox-neutrality) are selectively attained. However, related systems have not been described to the best of our knowledge.

Cp*Rh(III)-catalyzed arene C–H activation followed by cyclization has served as a cornerstone for synthesizing cyclic structures [26–33]. The C–H activation of anilines has been well-explored for synthesis of heterocycles using unsaturated coupling partners [34–37]. We recently reported the integration of C–H activation and transfer hydrogenation (TH) in the coupling of anilines and enones under Ir(III) and Rh(III) catalysis, which afforded two reductive products (**E**, **F**) and one redox-neutral product (**D**, Scheme 1) [38]. We reasoned that the TH reduction can be extended to TH oxidation [39–41] or external oxidation. During our investigations on the coupling

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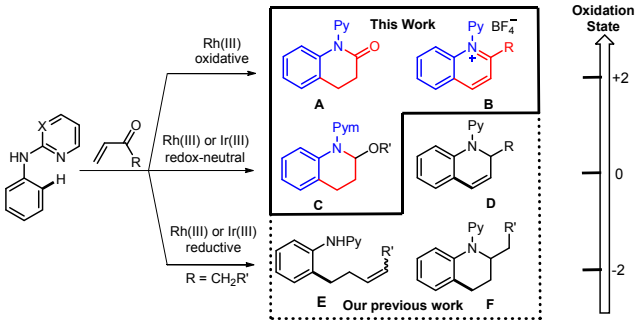
This work was supported by the National Nature Science Foundation of China (21525208, 21472186) and the fund for new technology of methanol conversion of Dalian Institute of Chemical Physics (Chinese Academy of Sciences).
DOI: 10.1016/S1872-2067(18)63134-1 | http://www.sciencedirect.com/science/journal/18722067 | Chin. J. Catal., Vol. 39, No. 11, November 2018



Scheme 1. Redox-switch in the coupling of anilines and acroleins/enones.

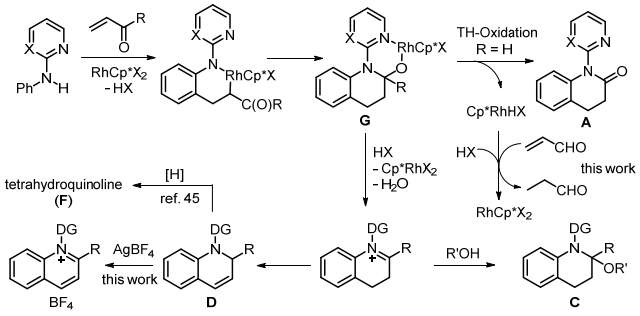
between the same anilines and acroleins or enones, we realized oxidative synthesis of two heterocycles, namely dihydroquinolones (**A**) and quinolinium salts (**B**). In addition, in the case of acrolein coupling partner, hemiaminal ether (**C**) was obtained via redox-neutral coupling in an alcoholic solvent (Scheme 1).

The C–H activation of anilines en route to hydroarylation of acrolein/enones and nucleophilic cyclization generates a Rh(III) alkoxide intermediate (**G**) which is a common intermediate for further transformations (Scheme 2). In the case of an acrolein, β-hydrogen elimination of **G** is proposed to furnish a dihydroquinolone (**A**) together with formation of a Cp*RhXH, which is a direct precursor of Cp*Rh(I) intermediate that can be reoxidized by an external oxidant or by the acrolein (via transfer hydrogenation). In fact, this β-hydrogen elimination has been realized for amide/lactam synthesis in related Rh(III)-catalyzed reactions of aldehydes [42–44]. Alternatively, the alkoxide intermediate **G** may undergo protonolysis and elimination of water to afford an iminium species that is prone to TH reduction [45] or nucleophilic addition. We now report these divergent couplings under substrate/condition control.

2. Experimental

2.1. General

All chemicals were obtained from commercial sources and were used as received unless otherwise noted. *N*-pyridylaniline [46], *N*-pyrimidylindole [47], and **2e** [48], were prepared by following the literature reports. All reactions were carried out using Schlenk techniques or in a nitrogen-filled glove box. ^{1}H and ^{13}C NMR spectra were recorded using $CDCl_3$ as a solvent on a bucker 400 MHz NMR spectrometer. The chemical shift is given in dimensionless δ values and is referenced relative to TMS in ^{1}H and ^{13}C NMR spectroscopy. All coupling constants (J) were reported in Hertz (Hz). Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m). HRMS data were obtained via ESI mode with a TOF mass analyzer. Column chromatography was performed on silica gel (300–400 mesh) with freshly distilled ethyl acetate (EA) and petroleum ether (PE).



Scheme 2. Diverse pathways of the coupling of anilines and acroleins/enones.

2.2. General procedure for the synthesis of compounds *3*, *4*, *6*

N-(2-pyrimidyl)anilines (**1**, 0.2 mmol), α,β-unsaturated ketones (**2**, 0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgBF_4$ (2.5 equiv), MeOH (3.0 mL) were charged into a Schlenk tube under a nitrogen atmosphere. The reaction mixture was stirred at 120 °C for 12 h. Then the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography using DCM/MeOH to afford compound **3**.

N-(2-pyridyl)anilines (**1**, 0.2 mmol), acrolein (**2f**, 0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), HOAc (2 equiv), $Cu(OAc)_2$ (0.3 equiv), and acetone (3.0 mL) were charged into a Schlenk tube under a nitrogen atmosphere. The reaction mixture was stirred at 40 °C for 12 h. Then the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography using EA/PE to afford compound **4**.

N-(2-pyrimidyl)anilines (**5**, 0.2 mmol), acrolein (**2f**, 0.4 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), HOAc (2 equiv), $Ni(OAc)_2{\cdot}4H_2O$ (30 mol%) and EtOH (3.0 mL) were charged into a Schlenk tube under a nitrogen atmosphere. The reaction mixture was stirred at 40 °C for 12 h. Then the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography using EA/PE to afford compound **6**.

2.3. Spectral data for products

3aa, brown solid (54.5 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.16 (d, J = 8.7 Hz, 1H), 8.81 (d, J = 3.6 Hz, 1H), 8.35–8.24 (m, 2H), 8.12 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.95–7.78 (m, 3H), 7.07 (d, J = 8.7 Hz, 1H), 3.10–2.99 (m, 1H), 2.83–2.72 (m, 1H), 1.38 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 151.0, 149.8, 148.6, 141.5, 139.8, 135.6, 130.5, 129.7, 128.2, 127.4, 123.5, 123.0, 119.4, 28.9, 12.6. HRMS: $[M\text{-}BF_4]^+$ calculated for $C_{16}H_{15}N_2$ 235.1230, found 235.1230.

3ab, yellow solid (56.4 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.19 (d, J = 8.6 Hz, 1H), 8.83 (d, J = 3.9 Hz, 1H), 8.35–8.29 (m, 2H), 8.10 (d, J = 8.6 Hz, 1H), 7.98–7.90 (m, 2H), 7.88–7.83 (m, 2H), 7.08 (d, J = 8.7 Hz, 1H), 3.06–2.97 (m, 1H), 2.75–2.66 (m, 1H), 1.81–1.72 (m, 2H), 1.27–1.18 (m, 4H), 0.81 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 150.8, 149.7, 148.5, 141.4, 139.7, 135.6, 130.5, 129.7, 128.1, 127.4, 123.6, 123.3, 119.4, 35.2, 31.4, 28.5, 22.0, 13.7. HRMS: $[M\text{-}BF_4]^+$ calculated for $C_{19}H_{21}N_2$ 277.1699, found 277.1697.