Chinese Journal of Catalysis 39 (2018) 138–145

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journal homepage: www.elsevier.com/locate/chnjc

Article

Copper-catalyzed tandem radical amination/1,2-carbon migration of allylic alcohols: Direct access to α-quaternary-β-amino ketones

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ARTICLE INFO

Article history:
Received 4 September 2017
Accepted 15 September 2017
Published 5 January 2018

Keywords:
Allylic alcohols
Nitrogen-centered radicals
1,2-Carbon migration
α-Quaternary-β-amino ketones
N-F regent

ABSTRACT

A novel nitrogen-centered radical-induced 1,2-carbon migration reaction of allylic alcohols has been developed. This method provides easy access to a variety of α-quaternary-β-amino ketones under mild reaction conditions. The reaction has a wide substrate scope and operational simplicity. Mechanistic studies suggest that 1,2-carbon migration is induced by regioselective nitrogen-centered radical addition to the alkene unit.

1. Introduction

Allylic alcohols are among the most versatile building blocks in organic synthesis, and their 1,2-carbon migration induced by radical or cation addition, e.g., in the semipinacol rearrangement, is a widely used and powerful method for constructing α-quaternary-β-functionalized carbonyl compounds [1–3]. Such compounds are important in organic synthesis, e.g., in the total synthesis of natural products; therefore the development of more efficient methods for their synthesis is needed [4–9]. Much effort has been devoted to investigating methods for the functionalization of allylic alcohols [10–43], such as halogenation [10–18], trifluoromethylation [19–26], sulfonylation [27], phosphorylation [28], and arylation [29–31]. These methods enable direct synthesis of various α-quaternary-β-functionalized ketones (Scheme 1, (a)). However, the aminative 1,2-carbon migration of allylic alcohols is challenging because of direct competition from nucleophilic substitution. In 2008, Tu and coworkers [44] developed a tandem aziridination/rearrangement reaction of allylic alcohols using a nitrene equivalent (Scheme 1, (b)). In 2014, the same group reported a radical azidative 1,2-carbon migration reaction of allylic silyl ethers (Scheme 1, (c)) [45]. Progress has been made in this field, but the development of an effective aminative carbonation of allylic alcohols via 1,2-carbon migration is still needed. We reasoned that facile generation of a nitrogen-centered radical under mild reaction conditions could be the key to this domino reaction.

Radical amination has emerged as a powerful tool for the

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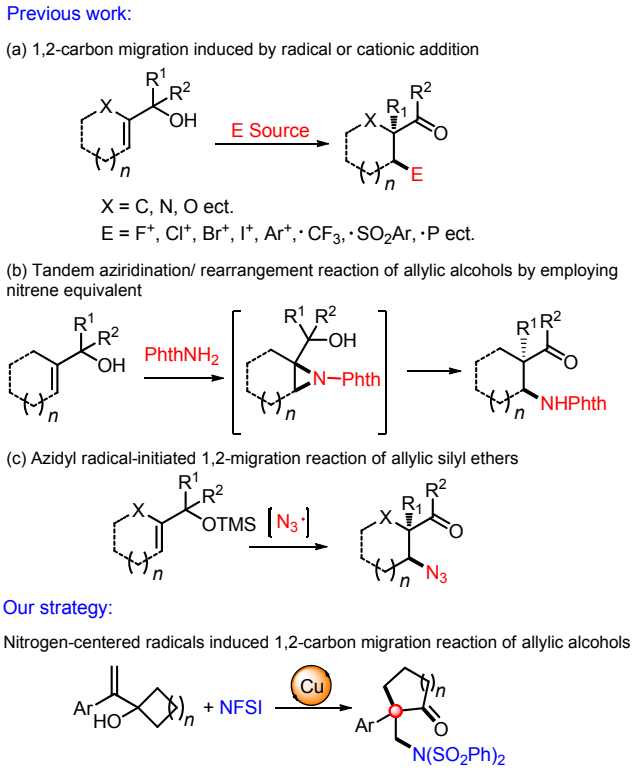
This work was supported by the National Natural Science Foundation of China (21372041), Changbai Mountain Scholarship Program, and the Fundamental Research Funds for the Central Universities (2412016KJ006).
DOI: 10.1016/S1872-2067(18)63028-1 | http://www.sciencedirect.com/science/journal/18722067 | Chin. J. Catal., Vol. 39, No. 1, January 2018



Scheme 1. Addition to C=C bond induced 1,2-carbon migration of allylic alcohols and derivatives.

synthesis of a range of bioactive nitrogen-containing molecules [46,47]. Studer [49,50], Kanai [51], and our group [53–58] have shown that *N*-fluorobenzenesulfonamide (NFSI) is an efficient and versatile nitrogen radical source for aminative functionalization of alkenes and alkynes [48–61]. Recently, Liu and coworkers [62] reported a novel copper-catalyzed enantioselective aminocyanation of alkenes using this reagent. It has been shown that a sterically hindered metal-stabilized nitrogen radical can be generated from NFSI under mild reaction conditions. On the basis of these pioneering studies, we reasoned that a radical semipinacol rearrangement of allylic alcohols could be triggered by addition of an in situ-generated nitrogen-centered radical to the alkene unit. While this manuscript was being prepared, Zhang and coworkers [63] reported a copper-catalyzed amination-induced 1,2-rearrangement of allylic alcohols. Here, we report a novel radical amination/ 1,2-carbon migration cascade, using an inexpensive copper catalyst, that enables rapid assembly of α-quaternary-β-amino ketones from readily available allylic alcohols (Scheme 1).

2. Experimental

2.1. General

All reagents were purchased from commercial suppliers and used without further purification. The reactions were monitored using thin-layer chromatography on 0.25 mm pre-coated silica-gel plates. UV light was used for visualization. Melting points (mps) were measured using a Büchi B-540 apparatus. ^{1}H NMR spectra were recorded at 25 °C using a Bruker 600 or Varian 500 MHz instrument. ^{13}C NMR spectra were recorded at 25 °C using a Bruker 150 or Varian 125 MHz instrument. Chemical shifts (δ) are given in parts per million (ppm) relative to the residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR). Coupling constants (J) are given in hertz. The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. High-resolution mass spectrometry (HRMS) was performed using a Brucker micrO-TOF instrument. The allylic alcohols **1** were synthesized using a previously published procedure [14,30].

2.2. General procedure for synthesis of compounds *3* and *4*

An allylic alcohol (0.2 mmol), N–F reagent (0.3 mmol), $Cu[(CH_3CN)_4PF_6]$ (0.02 mmol, 7.5 mg), BC (0.02 mmol, 7.2 mg), and anhydrous $CHCl_3$ (2 mL) were added to a flame-dried reaction tube equipped with a magnetic stirring bar in a nitrogen-filled glove box. The tube was sealed with a screw-cap and removed from the glove-box. The reaction mixture was stirred at 60 °C for 24.0 h. When the reaction was finished, the reaction mixture was cooled to room temperature and quenched with water. The mixture was extracted with dichloromethane (3 × 5.0 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified using column chromatography (petroleum ether/ethyl acetate 15:1 (v/v)) to give the corresponding product.

2.3. Spectral data for products

3a. White solid, mp 143–144 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, J = 7.8 Hz, 4H), 7.64 (t, J = 7.8 Hz, 2H), 7.48 (t, J = 7.8 Hz, 4H), 7.37 (dd, J = 7.8, 0.6 Hz, 2H), 7.34–7.31 (m, 2H), 7.26–7.24 (m, 1H), 4.25 (d, J = 16.2 Hz, 1H), 4.05 (d, J = 16.2 Hz, 1H), 2.60 (dd, J = 13.2, 6.0 Hz, 1H), 2.48–2.42 (m, 1H), 2.26 (dd, J = 19.2, 9.0 Hz, 1H), 2.18–2.11 (m, 1H), 1.97–1.92 (m, 1H), 1.63–1.56 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.8, 139.2, 138.3, 134.0, 129.0, 128.9, 128.6, 127.5, 127.0, 58.1, 53.3, 36.6, 32.3, 18.6. HRMS (ESI-TOF) (m/z): Calcd. for $C_{24}H_{23}NNaO_5S_2$ ([M + Na]$^+$) 492.0910, found 492.0914.

3b. Yellow liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, J = 7.8 Hz, 4H), 7.64 (t, J = 7.8 Hz, 2H), 7.48 (t, J = 7.8 Hz, 4H), 7.32–7.28 (m, 4H), 4.21 (d, J = 16.8 Hz, 1H), 4.00 (d, J = 16.2 Hz, 1H), 2.57 (dd, J = 13.2, 5.4 Hz, 1H), 2.49–2.44 (m, 1H), 2.26 (dd, J = 19.2, 9.0 Hz, 1H), 2.20–2.13 (m, 1H), 1.99–1.95 (m, 1H), 1.61–1.54 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 217.4, 138.3, 137.7, 134.1, 133.6, 129.1, 129.0, 128.6, 128.6, 57.6, 53.8, 36.5, 32.3, 18.6. HRMS (ESI-TOF) (m/z): Calcd. for $C_{24}H_{22}ClNNaO_5S_2$ ([M + Na]$^+$) 526.0520, found 526.0529.

3c. Yellow liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, J = 7.8 Hz, 4H), 7.64 (t, J = 7.8 Hz, 2H), 7.48 (t, J = 7.8 Hz, 4H), 7.36–7.34 (m, 2H), 7.03–6.99 (m, 2H), 4.22 (d, J = 16.2 Hz, 1H), 4.00 (d, J = 16.2 Hz, 1H), 2.58 (dd, J = 13.2, 6.0 Hz, 1H), 2.50–2.44 (m, 1H), 2.26 (dd, J = 19.2, 8.4 Hz, 1H), 2.18–2.13 (m, 1H), 1.99–1.94 (m, 1H), 1.62–1.54 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 217.6, 162.0 (J = 245.9 Hz), 138.3, 134.8 (J = 3.2 Hz), 134.1, 129.0,