Rh(III)-catalyzed regioselective intermolecular N-methylene Csp\(^3\)–H bond carbenoid insertion\(^\dagger\)

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A Rh(III)-catalyzed regioselective intermolecular carbenoid insertion into the N-methylene Csp\(^3\)–H bond of acyclic aliphatic amides has been achieved, taking advantage of bidentate–chelation assistance. This methodology has been successfully applied to a broad range of linear and branched-chain N-alkylamides, thus providing a practical method for the assembly of diverse beta-amino esters. Mechanism studies and density functional theory (DFT) calculations revealed that a singlet Fischer type carbene insertion via an outer-sphere pathway was involved in this N-methylene Csp\(^3\)–H bond carbenoid insertion.

Introduction

Alkyl C–H bond carbenoid functionalization is one of the most challenging topics for atom-economical C–C bond formations.\(^1\) Over the past few decades, transition-metal catalyzed intra- and intermolecular heteroatom-adjacent Csp\(^3\)–H carbenoid insertions have been well-established for assembling structurally complex molecules, but substrate-specific problems have not yet been overcome.\(^2\) In terms of the intermolecular version of N-adjacent Csp\(^3\)–H bond carbenoid insertion to acyclic amines, the existing transition metal catalytic systems only tolerate N-methyl Csp\(^3\)–H bonds instead of N-methylene Csp\(^3\)–H bonds (Scheme 1a).\(^2\) The intermolecular carbenoid insertion into the N-methylene Csp\(^3\)–H bonds of acyclic aliphatic amines is very difficult to achieve because of the delicate balance between steric and electronic factors.\(^3\)

Recently, chelation-assisted intermolecular Csp\(^3\)–H bond carbenoid functionalization has obtained a breakthrough via the “Inner-Sphere Pathway” (ISP); this strategy provides a powerful approach for site-selective aryl C–H carbenoid insertion. In this regard, Yu,\(^4\) Glorious,\(^5\) Rovis,\(^6\) Li\(^7\) and others successively reported that Rh(III) and Co(III)-catalyzed ortho aryl Csp\(^3\)–H cross-coupling reactions with diazo compounds could conveniently install C–C bonds into arenes by employing oximes, hydroxamic acids, pyridines or quaternary ammoniums as directing groups. In sharp contrast, ligand-directed alkyl Csp\(^3\)–H carbenoid functionalization remains almost undeveloped, owing to such bonds possessing a relatively smaller s-orbital contribution and larger bond dissociation energy.\(^10\) To date, only Martin and Zhou have ever reported that transition metal-catalyzed intermolecular Csp\(^3\)–H bond alkylation with diazo compounds could occur through the ISP using aryl bromides, arylamine N-oxides and quinoline as reaction platforms, but these tactics were limited to only primary methyl Csp\(^3\)–H bonds (Scheme 1b).\(^11\) Therefore, developing various types of methylene Csp\(^3\)–H carbenoid insertion remains challenging yet highly desirable. Very recently, we have accomplished a novel Ir(III)-catalyzed bidentate-assisted regioselective methylene Csp\(^3\)–H nitrene insertion,\(^12\) in which the “Outer-Sphere Pathway (OSP)”\(^4,12\) is involved in the transformation. Undoubtedly, the chelation-assisted OSP has already brought us a rising innovative concept, thus providing a promising approach to achieve versatile methylene Csp\(^3\)–H...
functionalizations. Herein, we report an unprecedented Rh(III)-catalyzed bidentate-assisted regioselective intermolecular carbendion insertion of N-methylene Csp3–H bonds via the OSP (Scheme 1c). This protocol constitutes a unique tool to rapidly build up complex linear beta-amino acid derivatives, which are among the most important precursors of beta-peptides and beta-lactams and feature in a large number of naturally occurring and unnatural compounds.

Results and discussion

We initiated our study by investigating the cross-coupling reaction of N-butyl-pyridine-2-carboxylic acid amide (1a) and z-diazo-beta-ketoester (2a) in the presence of metal catalysts including [Cp*IrCl2], Cp*Co(CO)I2, Cp*Co(MeCN)SbF5, RhCl3, Rh2(OAc)4 and [Cp3RhCl2] (5 mol%) and Ag2CO3 (20 mol%) in CH3CN at 100 °C for 24 h (see Table S-1 in ESI†). To our delight, screening of the catalysts quickly revealed that [Cp3RhCl2] could provide the coupling product 3a with a promising 47% yield (Table 1, entry 1), in which the C–H carbendion insertion occurred highly regioselectively at the N-methylene C–H bond. Unfortunately, other transition metal salts such as [Cp*IrCl2], Cp*Co(CO)I2, Rh2(OAc)4, etc. were not efficient at all. Then, various types of silver additive were evaluated (entries 3–7) and it was found that employing AgOAc as an additive could moderately improve the yield of 3a from 47% to 65% (compare entry 2 with 7, also see Table S-2 in ESI†). The reaction conversion could be further promoted when the additive could moderately improve the yield of 3a from 47% to 65% (compare entry 2 with 7, also see Table S-2 in ESI†). The reaction temperature resulted in worse results (entries 9 and 10).

With this protocol in hand, the scope of the Rh(III)-catalyzed N-methylene C–H carbendion insertion of N-butyl-pyridine-2-carboxylic acid amide (1a) was first investigated with a range of diazo compounds 2 (Table 2). As illustrated for 3a–3i, diacceptor- and donor/acceptor-substituted diazo compounds underwent smooth cross-coupling reactions with N-methylene C–H bonds to furnish beta-amino esters (3a–3i, 43–91% yields). Among them, alpha-diazo-beta-ketoesters participated in the transformation to produce alpha-acyl-beta-amino esters (3a and 3b, 89% and 43% yield, respectively). Moreover, various alpha-diazo-beta-arylesters are also applicable to the present transformation, leading to the formation of the corresponding alpha-aryl and beta-amino esters, in which the substituent on the aryl ring had an important effect on the yield of the reaction. These alpha-diazo-beta-arylesters with electron-deficient phenyl rings gave the products in moderate to excellent yields (3c–3h, 50–91% yields). On the contrary, compared with diazo-phenylacetic acid methyl ester (3i, 51% yield), when an electron-

Table 1 Optimization of reaction conditions

| Entry | Catalyst | Additive | Solvent | Yield (%) |
|-------|----------|----------|---------|-----------|
| 1     | Rh3(OAc)4 | Ag2CO3   | CH3CN   | 0         |
| 2     | [Cp*RhCl2] | Ag2CO3   | CH3CN   | 47        |
| 3     | [Cp*RhCl2] | AgClO4   | CH3CN   | –         |
| 4     | [Cp*RhCl2] | AgSbF5   | CH3CN   | 28        |
| 5     | [Cp*RhCl2] | AgBF4    | CH3CN   | 15        |
| 6     | [Cp*RhCl2] | AgNTf2   | CH3CN   | 63        |
| 7     | [Cp*RhCl2] | AgOAc    | CH3CN   | 65        |
| 8     | [Cp*RhCl2] | AgOAc    | TFE     | 89        |
| 9     | [Cp*RhCl2] | AgOAc    | TFE     | 69†       |
| 10    | [Cp*RhCl2] | AgOAc    | TFE     | 71†       |

† Unless otherwise noted, all of the reactions were carried out using N-butyl-pyridine-2-carboxylic acid amide (1a) (0.10 mmol) and diazo compound (2a) (0.20 mmol) with a metal catalyst (5.0 mol%) in the presence of a silver salt (20 mol%) in solvent (1.0 mL) at 100 °C for 24 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO2. † Isolated yield. †† TFE refers to 2,2,2-trifluoroethanol. † The reaction temperature is 80 °C. †† The reaction temperature is 110 °C.

Table 2 Substrate scope

| Entry | Catalyst | Additive | Solvent | Yield (%) |
|-------|----------|----------|---------|-----------|
| 3a    | Rh3(OAc)4 | Ag2CO3   | CH3CN   | 67%       |
| 3b    | Rh3(OAc)4 | Ag2CO3   | CH3CN   | 51%       |
| 3c    | Rh3(OAc)4 | Ag2CO3   | CH3CN   | 91%       |
| 3d    | Rh3(OAc)4 | Ag2CO3   | CH3CN   | 89%       |
| 3e    | Rh3(OAc)4 | Ag2CO3   | CH3CN   | 43%       |
| 3f    | Rh3(OAc)4 | Ag2CO3   | CH3CN   | 40%       |
| 3g    | Rh3(OAc)4 | Ag2CO3   | CH3CN   | 49%       |
| 3h    | Rh3(OAc)4 | Ag2CO3   | CH3CN   | 51%       |
| 3i    | Rh3(OAc)4 | Ag2CO3   | CH3CN   | 51%       |

† All of the reactions were carried out using amides (1) (0.10 mmol) and diazo compounds (2) (0.20 mmol) with [Cp3RhCl2] (5.0 mol%) in the presence of Ag2CO3 (20 mol%) in 2,2,2-trifluoroethanol (1.0 mL) at 100 °C for 24 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO2. † Isolated yield. †† d.r. values were determined by 1H NMR spectroscopy, please see ESI.
richer aryl group-containing diazo ester such as diazo-(4-methoxy-phenyl)-acetic acid methyl ester was used, an unexpected alkene 3k (2:1 = 3:1) was formed in 67% yield, and no desired beta-amino ester 3j was observed.

Subsequently, we prepared the 3- or 4-substituted pyridine-2-carboxylic acid butylamides, and investigated the substitution effect of pyridine moieties on N-methylene Csp<sup>3</sup>-H bond carbenoid insertion with 2-diazo-3-oxo-butric acid methyl ester 2a. It was found that introducing a methyl group or bromo group into the 3- or 4-position of the pyridine ring could lead to moderate yields of 3l and 3n (48%), and a pyridine ring with a strong electron-withdrawing group (–NO<sub>2</sub>) was not tolerated for this transformation (3m).

The scope of the present procedure with regard to different types of N-amido alkane has been further evaluated. Compared with the N-n-butyl-substituted amide (1a), the shorter or longer straight-chain alkylamine-based amides could be smoothly regioselectively installed a Csp<sup>3</sup>–Csp<sup>3</sup> bond into the alpha-position of the alkylamine moiety in 78–86% yields (3o–3r). Branched-chain 3-methyl-butylamine-based amides and phenylpropylamine- or phenylethylamine-based amides could also tolerate this reaction system and afforded structurally complex beta-amino acid derivatives 3s (76%), 3t (83%) and 3u (73%). Meanwhile, we also observed that the intermolecular N-methylene Csp<sup>3</sup>–H bond carbenoid insertion of 2-thiophen-3-yl-ethyamine-based amides also proceeded well to give a 66% yield of 3v, and thiophenyl C–H carbenoid insertion did not occur. However, N-benzyl-substituted amides made the transformation a little sluggish, possibly due to steric hindrance from the phenyl ring suppressing the N-methylene Csp<sup>3</sup>–H bond insertion (3w–3z and 3aa–3ad). To our surprise, the present protocol was also applicable to an alkynyl functional group-containing amidoalkane, in which the carbon–carbon double bond could be kept intact (3ad, 40% yield). More importantly, in addition to the N-allylamine, the N-cyclopropylmethylenelamine-based amide was also amenable to the reaction, furnishing the desired beta-cyclopropyl-beta-amino ester 3ae in a 49% yield. This transformation was not only limited to the N-methylene Csp<sup>3</sup>–H bond; Csp<sup>3</sup>–N-alkenylnitrene could also couple with diazoester 2a through an N-methylene Csp<sup>3</sup>–H bond carbenoid insertion to provide the target product 3af (46%). Unfortunately, pyridine-2-carboxylic acid (2-acetylamino-ethyl)-amide was not tolerated for this transformation, possibly due to the coordination between Rh(m) and 1,2-bisamide “N” inhibiting the Csp<sup>3</sup>–H bond carbenoid insertion (3ag, 0%). Finally, the post-synthetic utility of this transformation revealed that 2-pyrindyl carboxamide 3e could be smoothly converted into a N–H free beta-amino acid (4a) in a 67% yield via a one-pot process (see ESIF for more details).

Designed control experiments, as well as DFT studies (see ESIT for more details), were performed to elucidate the plausible reaction mechanism (Scheme 2). Treatment of N-butylbenzamidine (1y) or N,N-dibutyl-benzamidine (1z) with aldehydoo ester (2a) under our standard conditions did not provide the corresponding target products 5a or 5b (Scheme 2a and b), and thus demonstrated that the pyridyl group and amide “N” played a significant bichelate-directing role in enabling the N-methylene C–H carbenoid insertion. Meanwhile, when 1a was subjected to 1.0 equiv. of AcOD in the presence of diazo compound 2a, no H/D exchange was detected at the alpha- or beta-position of the beta-aminoester 3a (Scheme 2c). Although this experiment implied that an irreversible concerted metalation-deprotonation (CMD) process followed by metal protonation was possibly involved in this transformation, our DFT study further excluded an inner-sphere mechanism via bidentate-assisted N-methylene Csp<sup>3</sup>–H bond activation, which is required to overcome an activation free energy of 49.1 kcal mol<sup>−1</sup> (TS<sub>3</sub>, Fig. S-5, ESIF*) due to the three-membered ring strain. Moreover, treatment of d-1m (78% D) with 2a afforded the deuterated product d-3w, in which 81% D was inserted at both the alpha- and beta-positions of the beta-amino ester d-3w (Scheme 2d); this result clearly indicated that a two-electron carbenoid insertion into the Csp<sup>3</sup>–H bond occurred in the presence of bidentate-chelation assistance. DFT calculations (Fig. 1, detailed pathways are shown in Fig. S-5, ESIF†) were carried out to further confirm the carbenoid insertion process. In the Rh-carbenoid formation stage, the Rh-carbenoid is formed via transition state TS<sub>1</sub>, with a calculated activation free energy of 33.8 kcal mol<sup>−1</sup> (Cat → TS<sub>1</sub>). Subsequently, we further evaluated both the singlet and the triplet carbenoid insertion pathways. The corresponding DFT results suggest that the carbenoid insertion proceeds in a singlet Fischer type carbene manner (21.9 kcal mol<sup>−1</sup>, TS<sub>2a</sub>–a; −2.5 kcal mol<sup>−1</sup>, TS<sub>2b</sub>–b), and the triplet pathway through radical recombination is less feasible due to the high activation free energy (43.4 kcal mol<sup>−1</sup>, TS<sub>2c</sub>–a). The singlet carbenone pathway was further confirmed by the control experiment (Scheme 2g), in which using TEMPO (1.0 equiv.) did not significantly decrease the reaction yield (91% of 3a).
outer-sphere pathway, successively producing the corresponding imine intermediate C and Rh[n] complex D. Further protonization of complex D furnishes the desired beta-amino ester 3p with the regeneration of the Rh(n) catalyst.

Conclusions

In summary, we have developed the first Rh(n)-catalyzed intermolecular N-methylene Csp³-H bond carbenoid insertion of acyclic aliphatic amides with high regioselectivity. In these systems, bidentate-chelation acts as a unique platform to enable the cross-coupling of N-methylene Csp³-H bonds with diazo compounds through the “Outer-Sphere Pathway”. This strategy could have broad implications on future research directions on selective Csp³-H functionalization. Moreover, this reaction tolerates a broad scope of substrates and provides an effective approach to diverse beta-amino esters. Further efforts to achieving an asymmetric version of this transformation are underway.

Conflicts of interest

There are no conflicts to declare.

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17 Rh(m)-catalyzed Csp3-H bond carbenoid insertion is only selective for the N-methylene Csp3-H bond. N-methyl pyridine-2-carboxylic amide (1x) could not tolerate the reaction conditions.
18 It should be noted that starting materials 1y, 1z and 2a were almost completely recovered, and also no dimers derived from diazo compound 2a were detected.
19 We also ran the H/D exchange experiment in TF3CD2OD (1.0 mL) instead of the solvent system (AcOD/CH3CN, Scheme 2c), and we still did not observe H/D exchange at the alpha- or beta-position of the beta-aminoester 3a, please see the ESI† for details.