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Rh(III)-catalyzed regioselective intermolecular *N*-methylene Csp³-H bond carbenoid insertion†

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A Rh(III)-catalyzed regioselective intermolecular carbenoid insertion into the *N*-methylene Csp³-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 Csp³-H bond carbenoid insertion.

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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 Csp³-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 Csp³-H bond carbenoid insertion to acyclic amines, the existing transition metal catalytic systems only tolerate *N*-methyl Csp³-H bonds instead of *N*-methylene Csp³-H bonds (Scheme 1a).^{2a} The intermolecular carbenoid insertion into the *N*-methylene Csp³-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 Csp²-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,⁵ Glorious,⁶ Rovis,⁷ Li⁸ and others⁹ successively reported that Rh(III) and Co(III)-catalyzed ortho aryl Csp²-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 Csp³-H carbenoid functionalization remains almost

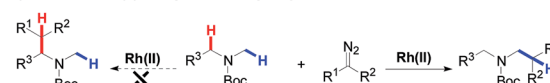
undeveloped, owing to such bonds possessing a relatively smaller *s*-orbital contribution and larger bond dissociation energy.¹⁰ To date, only Martin and Zhou have ever reported that transition metal-catalyzed intermolecular Csp³-H bond alkylation with diazo compounds could occur through the ISP using aryl bromides, arylamine *N*-oxides and quinoline as reaction platforms, but these tactics were limited to only primary methyl Csp³-H bonds (Scheme 1b).¹¹ Therefore, developing various types of methylene Csp³-H carbenoid insertion remains challenging yet highly desirable. Very recently, we have accomplished a novel Ir(III)-catalyzed bidentate-assisted regioselective methylene Csp³-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 Csp³-H

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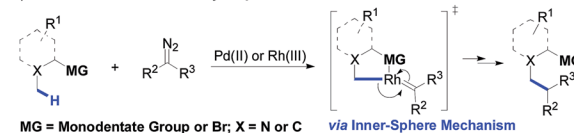
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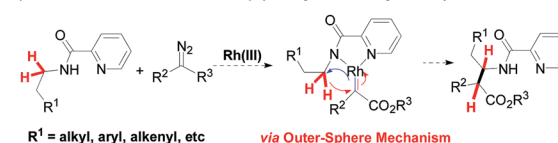
a) Traditional Rh(II)-catalyzed *N*-methyl Csp³-H bond carbenoid insertion



b) Monodentate-assisted methyl Csp³-H bond carbenoid insertion



c) This work: Bidentate-assisted Rh(III)-catalyzed *N*-methylene Csp³-H bond carbenoid insertion



Scheme 1 Approaches to versatile Csp³-H carbenoid insertion.



functionalizations. Herein, we report an unprecedented Rh(III)-catalyzed bidentate-assisted regioselective intermolecular carbenoid 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-lactams¹³ and feature in a large number of naturally occurring and unnatural compounds.¹⁴

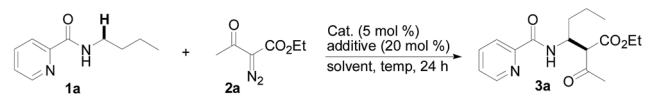
Results and discussion

We initiated our study by investigating the cross-coupling reaction of *N*-butyl-pyridine-2-carboxylic acid amide (**1a**) and α -diazo- β -ketoester (**2a**) in the presence of metal catalysts including [Cp*IrCl₂]₂, Cp*Co(CO)I₂, Cp*Co(MeCN)₃SbF₆, RhCl₃, Rh₂(OAc)₄ and [Cp*RhCl₂]₂ (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 [Cp*RhCl₂]₂ could provide the coupling product **3a** with a promising 47% yield (Table 1, entry 2), in which the C-H carbenoid insertion occurred highly regioselectively at the *N*-methylene C-H bond. Unfortunately, other transition metal salts such as [Cp*IrCl₂]₂, 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 transformation was conducted in TFE, which delivered an 89% yield of **3a** (entry 8); however, switching to other solvents such as 1,4-dioxane or DMSO led to a significantly lower coupling efficiency (see Table S-3 in ESI†). Also, lowering or increasing 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 carbenoid 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-

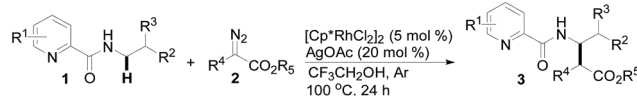
Table 1 Optimization of reaction conditions^a

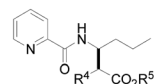
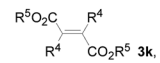
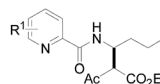
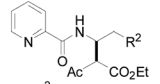
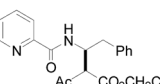
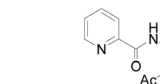
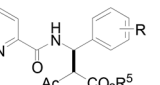
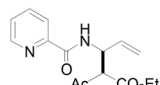
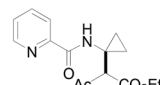
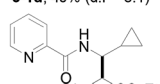


| Entry | Catalyst | Additive | Solvent | Yield ^b (%) |
|-------|--------------------------------------|---------------------------------|--------------------|------------------------|
| 1 | Rh ₂ (OAc) ₄ | Ag ₂ CO ₃ | CH ₃ CN | 0 |
| 2 | [Cp*RhCl ₂] ₂ | Ag ₂ CO ₃ | CH ₃ CN | 47 |
| 3 | [Cp*RhCl ₂] ₂ | AgClO ₄ | CH ₃ CN | — |
| 4 | [Cp*RhCl ₂] ₂ | AgSbF ₆ | CH ₃ CN | 28 |
| 5 | [Cp*RhCl ₂] ₂ | AgBF ₄ | CH ₃ CN | 15 |
| 6 | [Cp*RhCl ₂] ₂ | AgNTf ₂ | CH ₃ CN | 63 |
| 7 | [Cp*RhCl ₂] ₂ | AgOAc | CH ₃ CN | 65 |
| 8 | [Cp*RhCl ₂] ₂ | AgOAc | TFE ^c | 89 |
| 9 | [Cp*RhCl ₂] ₂ | AgOAc | TFE | 69 ^d |
| 10 | [Cp*RhCl ₂] ₂ | AgOAc | TFE | 71 ^e |

^a 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. ^b Isolated yield. ^c TFE refers to 2,2,2-trifluoroethanol. ^d The reaction temperature is 80 °C. ^e The reaction temperature is 110 °C.

Table 2 Substrate scope^{a,b,c}



| | |
|---|--|
|  3a , R ⁴ = CH ₃ CO, R ⁵ = Et, 89% (d.r. = 8:1) 3b , R ⁴ = PhCO, R ⁵ = Et, 43% (d.r. = 12:1) 3c , R ⁴ = 4-NO ₂ -C ₆ H ₄ , R ⁵ = Me, 83% (d.r. = 3:1) 3d , R ⁴ = 3-NO ₂ -C ₆ H ₄ , R ⁵ = Me, 65% (d.r. = 2.5:1) 3e , R ⁴ = 4-CF ₃ -C ₆ H ₄ , R ⁵ = Me, 91% (d.r. = 2:1) 3f , R ⁴ = 4-CN-C ₆ H ₄ , R ⁵ = Me, 82% (d.r. = 2.5:1) 3g , R ⁴ = 4-Br-C ₆ H ₄ , R ⁵ = Me, 50% (d.r. = 2:1) 3h , R ⁴ = 4-Cl-C ₆ H ₄ , R ⁵ = Me, 62% (d.r. = 1.7:1) 3i , R ⁴ = Ph, R ⁵ = Me, 51% (d.r. = 1.7:1) 3j , R ⁴ = 4-MeO-Ph, R ⁵ = Me, 0%  3k , R ⁴ = CO ₂ R ⁵ , R ⁵ = Me, 67% (Z/E = 3:1) |  3l , R ¹ = 4-Br, 48% (d.r. = 12:1) 3m , R ¹ = 4-NO ₂ , 0% 3n , R ¹ = 3-Me, 48% (d.r. = 2:1)  3o , R ² = H, 83% (d.r. = 10:1) 3p , R ² = Me, 86% (d.r. = 10:1) 3q , R ² = <i>n</i> -propyl, 82% (d.r. = 10:1) 3r , R ² = <i>n</i> -butyl, 78% (d.r. = 10:1) 3s , R ² = <i>i</i> -propyl, 76% (d.r. = 9:1) 3t , R ² = Bn, 83% (d.r. = 9:1) |
|  3u , 73% (d.r. = 8:1) |  3v , 66% (d.r. = 10:1) |
|  3w , R = 4-H, R ⁵ = Et, 51% (d.r. = 3:1) 3x , R = 4-Me, R ⁵ = Et, 63% (d.r. = 2:1) 3y , R = 3-Me, R ⁵ = Et, 30% (d.r. = 3:1) 3z , R = 2-Me, R ⁵ = Et, 25% (d.r. = 2:1) 3-1a , R = 4-OMe, R ⁵ = Et, 47% (d.r. = 3:1) 3-1b , R = 4-Cl, R ⁵ = Et, 45% (d.r. = 4:1) 3-1c , R = 4-CF ₃ , R ⁵ = CH ₂ CF ₃ , 40% (d.r. = 10:1) |  3-1d , 40% (d.r. = 8:1)  3-1f , 46% (d.r. = 2:1)  3-1g , 49% (d.r. = 7:1) 3-1g , 0% |

^a All of the reactions were carried out using amides (**1**) (0.10 mmol) and diazo compounds (**2**) (0.20 mmol) with [Cp*RhCl₂]₂ (5.0 mol%) in the presence of AgOAc (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. ^b Isolated yield. ^c d.r. values were determined by ¹H NMR spectroscopy, please see ESI.

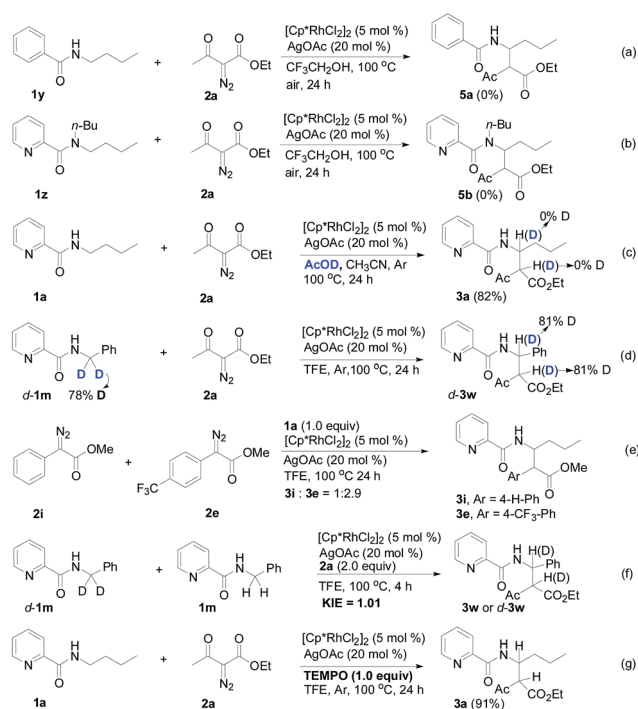


richer aryl group-containing diazo ester such as diazo-(4-methoxy-phenyl)-acetic acid methyl ester was used, an unexpected alkene **3k** (*Z/E* = 3 : 1) was formed in 67% yield, and no desired beta-amino ester **3j** was observed.

Subsequently, we prepared the 3- or 4-substituted pyridine-2-carboxylic acid butylamides, and investigated the substitution effect of pyridine moieties on *N*-methylene Csp³-H bond carbenoid insertion with 2-diazo-3-oxo-butiric 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 (–NO₂) 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 Csp³-Csp³ 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 Csp³-H bond carbenoid insertion of 2-thiophen-3-yl-ethylamine-based amides also proceeded well to give a 66% yield of **3v**, and thiophenyl C–H carbenoid insertion did not occur.¹⁵ However, *N*-benzyl-substituted amides made the transformation a little sluggish, possibly due to steric hindrance from the phenyl ring suppressing the *N*-methylene Csp³-H bond insertion (**3w–3z** and **3-1a–3-1c**). To our surprise, the present protocol was also applicable to an alkenyl functional group-containing amidoalkane, in which the carbon–carbon double bond could be kept intact (**3-1d**, 40% yield).¹⁶ More importantly, in addition to the *N*-allylamine, the *N*-cyclopropylmethyleneamine-based amide was also amenable to the reaction, furnishing the desired beta-cyclopropyl-beta-amino ester **3-1e** in a 49% yield. This transformation was not only limited to the *N*-methylene Csp³-H bond;¹⁷ *N*-cyclopropylamide could also couple with diazoester **2a** through an *N*-methylene Csp³-H bond carbenoid insertion to provide the target product **3-1f** (46%). Unfortunately, pyridine-2-carboxylic acid (2-acetyl-amino-ethyl)-amide was not tolerated for this transformation, possibly due to the coordination between Rh(III) and 1,2-bisamide “N” inhibiting the Csp³-H bond carbenoid insertion (**3-1g**, 0%). Finally, the post-synthetic utility of this transformation revealed that 2-pyridyl 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 ESI† for more details).

Designed control experiments, as well as DFT studies (see ESI† for more details), were performed to elucidate the plausible reaction mechanism (Scheme 2). Treatment of *N*-butylbenzamide (**1y**) or *N,N*-dibutylbenzamide (**1z**) with alpha-diazo ester (**2a**) under our standard conditions did not provide the corresponding target products **5a** or **5b** (Scheme 2a and b),¹⁸ and thus demonstrated that the pyridyl group and amide “N” played a significant bichelate-directing role in



Scheme 2 Preliminary mechanism studies.

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-amino ester **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,¹⁹ our DFT study further excluded an inner-sphere mechanism *via* bidentate-assisted *N*-methylene Csp³-H bond activation, which is required to overcome an activation free energy of 49.1 kcal mol^{−1} (**TS3**, Fig. S-5, ESI†) 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 Csp³-H bond occurred in the presence of bidentate-chelation assistance. DFT calculations (Fig. 1, detailed pathways are shown in Fig. S-5, ESI†) were carried out to further confirm the carbenoid insertion process. In the Rh-carbenoid formation stage, the Rh-carbenoid is formed *via* transition state **TS1**, with a calculated activation free energy of 33.8 kcal mol^{−1} (**Cat** → **TS1**). 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^{−1}, **TS2_{s-a}**; −2.5 kcal mol^{−1}, **TS2_{s-b}**), and the triplet pathway through radical recombination is less feasible due to the high activation free energy (43.4 kcal mol^{−1}, **TS2_{t-a}**). The singlet carbene 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**).



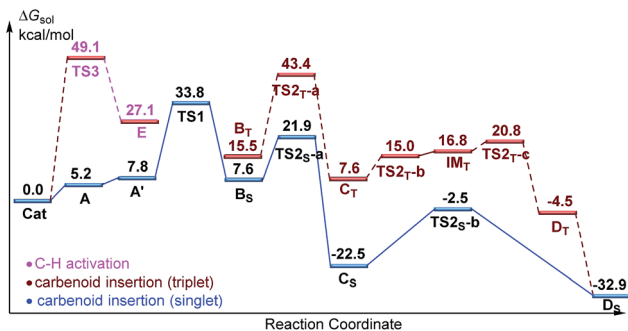


Fig. 1 The free energy profiles for the Rh(III)-catalyzed regioselective *N*-methylene Csp³-H bond carbenoid functionalization. The free energies are reported in kcal mol⁻¹ at the M06-L/BSII/SMD(2,2,2-trifluoroethanol)//M06-L/BSI level of theory.

The *N*-methylene C-H carbenoid insertion between alpha-aryl-alpha-diazo esters differing in electronic effects indicates that an electron-deficient diazo compound tended to form a rhodium carbene at a relatively higher rate (Scheme 2e). Moreover, a competitive cross-coupling of an equimolar mixture of **d-1m** and **1m** with alpha-diazo ester **2a** also gave a k_H/k_D value of 1.01 on the basis of the ¹H NMR spectrum (Scheme 2f), suggesting that C-H bond carbenoid insertion did not involve the rate-limiting step of this transformation. These results are further supported by our DFT data, which demonstrated that the formation of Rh-carbenoid *via* **TS1** ($\Delta G^\ddagger = 33.8$ kcal mol⁻¹) should be the rate-determining step.

A mechanism rationale coherent with these results and the DFT studies is proposed in Scheme 3. The initial coordination of the pyridyl nitrogen and amide nitrogen of substrate **1f** to an active Rh(III) catalyst affords complex **A**. Subsequent interaction of complex **A** with diazo compound **2a** is followed by denitrogenation to generate Rh carbene species **B**. The rhodium complex **B** undergoes a bichelate-assisted singlet Fischer type carbenoid insertion into the *N*-methylene Csp³-H bond *via* an

outer-sphere pathway, successively producing the corresponding imine intermediate **C** and Rh(III) complex **D**. Further protonation of complex **D** furnishes the desired beta-amino ester **3p** with the regeneration of the Rh(III) catalyst.

Conclusions

In summary, we have developed the first Rh(III)-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

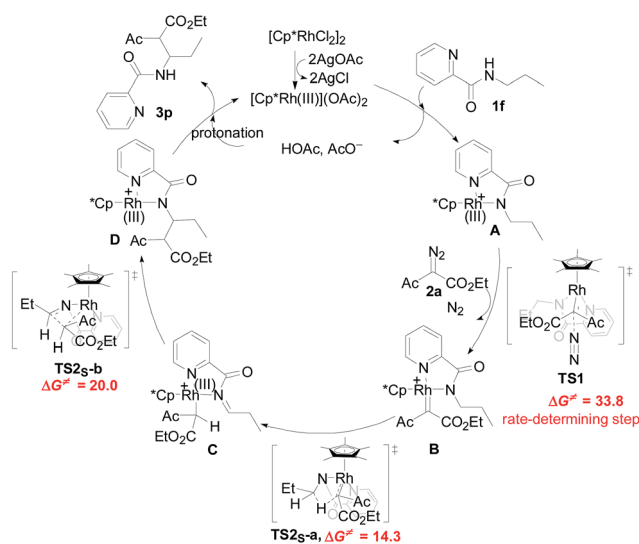
There are no conflicts to declare.

Acknowledgements

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Notes and references

- For selected reviews, see: (a) H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861; (b) H. M. L. Davies and Y. Lian, *Acc. Chem. Res.*, 2012, **45**, 923.
- For the cross-coupling reaction of diazo compounds with *N*-methyl Csp³-H bonds of linear aliphatic amines, see: (a) H. M. L. Davies and C. Venkataramani, *Angew. Chem., Int. Ed.*, 2002, **41**, 2197; (b) H. M. L. Davies and Q. Jin, *Org. Lett.*, 2004, **6**, 1769; (c) H. M. L. Davies and A. Ni, *Chem. Commun.*, 2006, 3110. For the cross-coupling reaction of diazo compounds with *N*-methylene Csp³-H bonds of cyclic amines, see: (d) H. M. L. Davies, C. Venkataramani, T. Hansen and D. W. Hopper, *J. Am. Chem. Soc.*, 2003, **125**, 6462; (e) H. M. L. Davies, T. Hansen, D. W. Hopper and S. A. Panaro, *J. Am. Chem. Soc.*, 1999, **121**, 6509; (f) J. M. Axten, R. Ivy, L. Krim and J. D. Winkler, *J. Am. Chem. Soc.*, 1999, **121**, 6511. For the cross-coupling reaction of diazo compounds with *O*-adjacent Csp³-H bonds of ethers, see: (g) D. M. Guptill and H. M. L. Davies, *J. Am. Chem. Soc.*, 2014, **136**, 17718; (h) H. M. L. Davies and T. Hansen, *J. Am. Chem. Soc.*, 1997, **119**, 9075.
- (a) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (b) S. M. Nicolle, W. Lewis, C. J. Hayes and C. J. Moody, *Angew. Chem., Int. Ed.*, 2016, **55**, 3749; (c) K. Liao,



Scheme 3 Proposed reaction mechanism.



- S. Negretti, D. G. Musaev, J. Bacsá and H. M. L. Davies, *Nature*, 2016, **533**, 230.
- 4 (a) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (b) K. Shin, H. Kim and S. Chang, *Acc. Chem. Res.*, 2015, **48**, 1040; (c) S. H. Park, J. Kwak, K. Shin, J. Ryu, Y. Park and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 2492.
- 5 W.-W. Chan, S.-F. Lo, Z. Zhou and W.-Y. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 13565.
- 6 D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert and F. Glorious, *Angew. Chem., Int. Ed.*, 2015, **54**, 4508.
- 7 T. K. Hyster, K. E. Ruhl and T. Rovis, *J. Am. Chem. Soc.*, 2013, **135**, 5364.
- 8 S. Yu, S. Liu, Y. Lan, B. Wan and X. Li, *J. Am. Chem. Soc.*, 2015, **137**, 1623.
- 9 (a) J. Jeong, P. Patel, H. Hwang and S. Chang, *Org. Lett.*, 2014, **16**, 4598; (b) J. Wang, M. Wang, K. Chen, S. Zha, C. Song and J. Zhu, *Org. Lett.*, 2016, **18**, 1178; (c) Z. Liu and J. Wang, *J. Org. Chem.*, 2013, **78**, 10024.
- 10 (a) D. G. Musaev and S. B. Blakey, *Organometallics*, 2012, **31**, 4950; (b) J. Xie, C. Pan, A. Abdukader and C. Zhu, *Chem. Soc. Rev.*, 2014, **43**, 5245.
- 11 (a) Á. Gutiérrez-Bonet, F. Juliá-Hernández, B. de Luis and R. Martín, *J. Am. Chem. Soc.*, 2016, **138**, 6384; (b) B. Zhou, Z. Chen, Y. Yang, W. Ai, H. Tang, Y. Wu, W. Zhu and Y. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 12121; (c) W. Hou, Y. Yang, Y. Wu, H. Feng, Y. Li and B. Zhou, *Chem. Commun.*, 2016, **52**, 9672.
- 12 X. Xiao, C. Hou, Z. Zhang, Z. Ke, J. Lan, H. Jiang and W. Zeng, *Angew. Chem., Int. Ed.*, 2016, **55**, 11897.
- 13 For selected examples, see: (a) T. N. Salzmán, R. W. Ratcliffe, B. G. Christensen and F. A. Bouffard, *J. Am. Chem. Soc.*, 1980, **102**, 6161; (b) D. Seebach, S. Abele, K. Gademann and B. Jaun, *Angew. Chem., Int. Ed.*, 1999, **38**, 1595; (c) Z. Juaristi, D. Quintana and J. Escalante, *Aldrichimica Acta*, 1994, **27**, 3.
- 14 For selected reviews, see: (a) R. M. Williams and J. A. Hendrix, *Chem. Rev.*, 1992, **92**, 889; (b) S. France, A. Weatherwax, A. E. Taggi and T. Lectka, *Acc. Chem. Res.*, 2004, **37**, 592; (c) G. P. Pollini, S. Benetti, C. De Risi and V. Zanirato, *Chem. Rev.*, 2006, **106**, 2434; (d) Y.-F. Wang, Q.-W. Shi, M. Dong, H. Kiyota, Y.-C. Gu and B. Cong, *Chem. Rev.*, 2011, **111**, 7652.
- 15 For selected examples, see: (a) R. J. Gillespie, J. Murray-Rust, P. Murray-Rust and A. E. A. Porter, *Tetrahedron*, 1981, **37**, 743; (b) T. Bowles, R. J. Gillespie, A. E. A. Porter, J. A. Rechka and H. S. Rzepa, *J. Chem. Soc., Perkin Trans. 1*, 1988, **4**, 803.
- 16 For selected examples, see: (a) R. Sambasivan and Z. T. Ball, *Angew. Chem., Int. Ed.*, 2012, **51**, 8568; (b) L. Gao, G.-S. Hwang and D. H. Ryu, *J. Am. Chem. Soc.*, 2011, **133**, 20708.
- 17 Rh(III)-catalyzed Csp³-H bond carbenoid insertion is only selective for the *N*-methylene Csp³-H bond. *N*-methyl pyridine-2-carboxylic acid 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.

