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Ru(II)-Pheox catalyzed N–H insertion reaction of diazoacetamides: synthesis of N-substituted α-aminoamides

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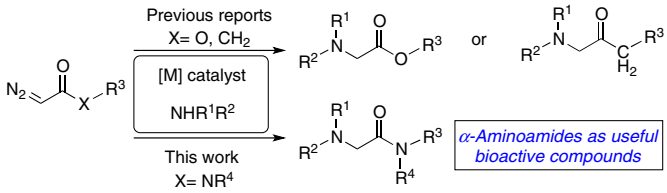
ABSTRACT

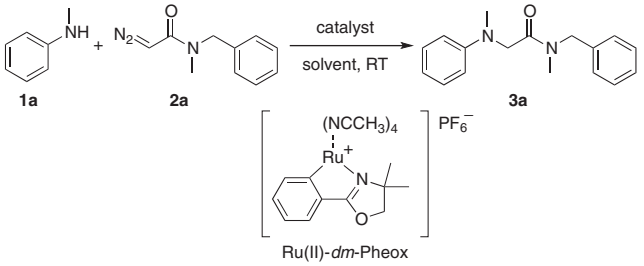
An efficient protocol for the preparation of α-aminoamides was developed via the Ru(II)-*dm*-Pheox catalyzed N–H insertion reaction of various diazoacetamides with several amines, including aniline. This catalytic N–H insertion reaction was also applied to the synthesis of 2-(2-methylquinolin-4-ylamino)-*N*-phenylacetamide, a potential antileishmanial agent.

α-Aminoamide structural moieties are found in a wide range of naturally occurring organic compounds and pharmaceuticals.[1] α-Aminoamides have been widely employed as intermediates,[2] organocatalysts,[3] and catalyst ligands[4] in organic synthesis. Hence, numerous methods for the construction of α-aminoamides have been developed in the past decade.[5] Traditionally, α-aminoamides are prepared by hydrolysis of the α-aminonitriles synthesized via the Strecker reaction,[6] but the drawbacks of this approach include toxicity issues such as HCN which must be generated in situ from cyanide salts and the requirement of harsh reaction conditions. Nucleophilic substitutions of amino acid derivatives and/or α-halogenated amides with amines are often employed for the synthesis of α-aminoamides, but the synthesis of *N*-aryl-substituted α-aminoamides has not been attempted frequently because the arylamines



Scheme 1. Transition-metal-catalyzed N–H insertion of α-diazocarbonyl compounds into amine derivatives.

Table 1
Optimization of catalytic N–H insertion reaction of diazoacetamide **2a** with *N*-methylaniline **1a**[a]



Entry	Catalyst	Solvent	Time	Yield[b] (%)
1	Ru(II)-*dm*-Pheox	Toluene	10 min	73
2	Ru(II)-*dm*-Pheox	H_2O	30 min	77
3	Ru(II)-*dm*-Pheox	CH_3OH	20 h	70
4	Ru(II)-*dm*-Pheox	CH_3OH	24 h	78
5	Ru(II)-*dm*-Pheox	THF	5 min	89
6	Ru(II)-*dm*-Pheox	Et_2O	10 min	80
7	Ru(II)-*dm*-Pheox	Acetone	5 min	89
8	Ru(II)-*dm*-Pheox	CH_2Cl_2	5 min	97
9[c]	Ru(II)-*dm*-Pheox	CH_2Cl_2	5 min	89
10[d]	$Rh_2(OAc)_4$	CH_2Cl_2	5 min	61
11[d]	CuI	CH_2Cl_2	48 h	42

[a] Performed at RT using 0.5 mol % of catalyst in Ar atmosphere with 2 equiv *N*-methylaniline **1a** and *N*-benzyl-*N*-methyldiazoacetamide **2a**.
[b] Isolated yield.
[c] Carried out with 1 equiv of *N*-methylaniline **1a**.
[d] Carried out with 5 mol % of catalyst.

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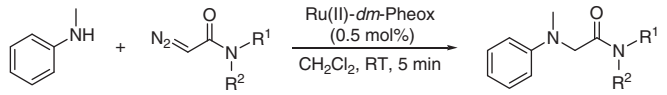
Table 2
Ru(II)-*dm*-Pheox catalyzed N–H insertion reaction of *N*-methylaniline **1a** with various diazoacetamides **2a–e**[a]



1a (2 equiv) **2a-e** **3a-e**

Entry	Diazoacetamide (R^1, R^2)	Product	Yield[b] (%)
1	**2a** (Bn, Me)	**3a**	97
2	**2b** (Bn, H)	**3b**	82
3	**2c** (Bn, Bn)	**3c**	84
4[c]	**2d** (Ph, H)	**3d**	93
5	**2e** (Et, Et)	**3e**	89

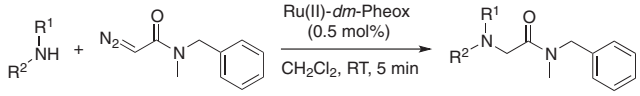
[a] Performed at RT using 0.5 mol % Ru(II)-*dm*-Pheox in Ar atmosphere with 2 equiv *N*-methylaniline **1a** and diazoacetamides **2a–e**.
[b] Isolated yield.
[c] Because diazoacetamide **2d** couldn't dissolve in CH_2Cl_2, thus we used acetone as the solvent.

precursors have low nucleophilicity.[7] Therefore, the development of novel efficient synthetic routes to N-substituted α-aminoamides is highly desirable.

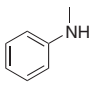
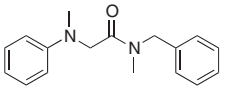
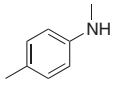
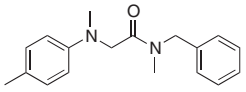
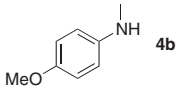
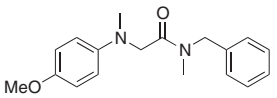
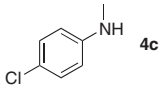
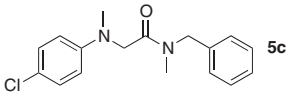
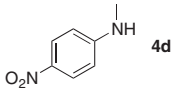
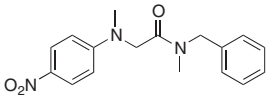
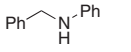
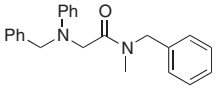
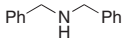
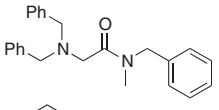
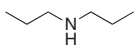
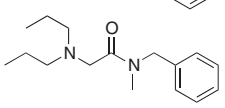
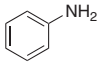
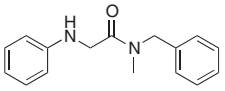
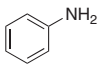
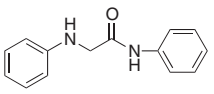
Among the various methods for C–N bond formation, insertion of an α-diazocarbonyl compound into an N–H bond is one of the straightforward routes to α-amino acid derivatives.[8] While there are numerous reports on the successful synthesis of α-aminoketones and α-aminoesters from diazoketones and diazoesters, respectively, there is no report on the use of diazoacetamide for the synthesis of α-aminoamides by N–H insertion (Scheme 1), except for that by Muthusamy and co-workers on the Rh_2-based N–H insertion of 3-diazopiperidin-2-ones.[9] Herein, we report an efficient protocol for the preparation of N-substituted α-aminoamides through the Ru(II)-catalyzed N–H insertion of diazoacetamides into amine derivatives.

The present study on the N–H insertion reaction of diazoacetamides, which would be a powerful tool for constructing α-aminoamides, was inspired by our previous study on the efficient use of

Table 3
Ru(II)-*dm*-Pheox catalyzed N–H insertion of diazoacetamide **2a** into various amines **1a** and **4a–h**



1a, 4a-h (2 equiv) **2a** **3a, 5a-i**

Entry	Amine	Product	Yield[a] (%)
1	 **1a**	 **3a**	97
2	 **4a**	 **5a**	98
3	 **4b**	 **5b**	94
4	 **4c**	 **5c**	90
5	 **4d**	 **5d**	48
6	 **4e**	 **5e**	95
7	 **4f**	 **5f**	96
8	 **4g**	 **5g**	92
9[b]	 **4h**	 **5h**	78
10[c]	 **4h**	 **5i**	85

[a] Isolated yield.
[b] Reaction was carried out using 3 mol % Ru(II)-*dm*-Pheox for 1 h because a long reaction time was required when using 0.5 mol % of the catalyst.
[c] Performed in acetone for 30 min using diazoacetamide **2d**.

Ru(II)-Pheox catalyst in the carbene transfer reactions of diazoacetates to furnish cyclopropanes.[10]

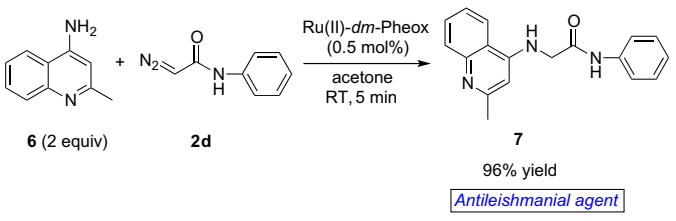
Initially, we evaluated the catalytic activity of Ru(II)-*dm*-Pheox catalyst[11] in various solvents for the intermolecular N–H insertion reaction of *N*-methylaniline **1a** with *N*-benzyl-*N*-methyldiazoacetamide **2a**, as shown in Table 1. Dichloromethane was the best solvent (Table 1, entry 8) since the reaction in this case gave **3a** in 97% yield, in the presence of 0.5 mol % Ru(II)-*dm*-Pheox catalyst. Interestingly, the catalyst could afford α-aminoamide **3a** in high yield (77%) even in water at room temperature (Table 1, entry 2). The yield was slightly decreased when the reaction was performed with 1 equiv of *N*-methylaniline **1a** to diazoamide **2a** (entry 9). $Rh_2(OAc)_4$ and CuI also catalyzed the N–H insertion of diazoacetamide **2a** with *N*-methylaniline **1a** to give moderate yields (entries 10 and 11).

Under the optimized conditions, N–H insertion reactions with various N-substituted diazoacetamides were examined (Table 2). All the N-substituted diazoacetamides participated in the reaction to afford the corresponding α-aminoamides in high yields (82–97%) in 5 min. Further, the reactivity of the N–H insertion was largely unaffected even when diazoacetamide **2c** having two bulky benzyl substituents was used.

N–H insertion reactions of various amines, including secondary, aliphatic, and aromatic amines, with **2a** in the presence of Ru(II)-*dm*-Pheox (0.5 mol %) at room temperature were also examined, as shown in Table 3. Electron-donating and electron-withdrawing arylamine derivatives could easily undergo insertion reactions with **2a** to give the corresponding α-aminoamides in high yields (90–98%; entries 1–4 and 6). The only exception was the reaction with *p*-nitroaniline **4d**, in which case the product yield was low (48%) and dimers were formed (entry 5), probably because the electron density of *p*-nitroaniline is lower than that of the other arylamines shown in Table 3. Simple secondary amines such as dibenzyl and dipropyl amines also afforded the corresponding α-aminoamides in high yields (entries 7 and 8). Interestingly, aniline, which has lower nucleophilicity than do other primary and secondary amines, could be successfully used in the insertion reaction with diazoacetamides **2a** and **2d** to afford the corresponding α-aminoamides in high yields (entries 9 and 10).

Encouraged by the efficiency of the Ru(II)-*dm*-Pheox catalyzed N–H insertion reaction of diazoacetamides with amines, we sought to examine the utility of this method for the synthesis of 2-(2-methylquinolin-4-ylamino)-*N*-phenylacetamide **7**, which was reported to be a potential antileishmanial agent by Sahu et al. in 2002[12] (Scheme 2). We used 4-aminoquinaldine **6** as the amine substrate and carried out the N–H insertion with *N*-phenyldiazoacetamide **2d** in the presence of Ru(II)-*dm*-Pheox catalyst under the optimized conditions. The desired α-aminoamide **7** was obtained in high yield (96%) within a very short time (5 min).

In conclusion, we have established an efficient protocol for the preparation of N-substituted α-aminoamides through the Ru(II)-*dm*-Pheox catalyzed N–H insertion reaction of various diazoacetamides into several amines, including aniline. The method gives easy access to α-aminoamide derivatives, which are important building blocks for the synthesis of natural products and pharmaceuticals. In addition, we successfully used this catalytic N–H insertion reaction and obtained 2-(2-methylquinolin-4-ylamino)-*N*-phenylacetamide, a potential antileishmanial agent, in high yield (96%) within 5 min under mild reaction conditions.



Scheme 2. Synthesis of 2-(2-methylquinolin-4-ylamino)-*N*- phenylacetamide **7** via Ru(II)-*dm*-Pheox catalyzed N–H insertion of diazoacetamide **2d** into 4-aminoquinaldine **6**.

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Supplementary data

Supplementary data (experimental procedures, detailed product characterization data, compound spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.134.

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