RSC Advances

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Advances*, 2013, **3**, 13702

Received 7th June 2013,
Accepted 21st June 2013

DOI: 10.1039/c3ra42834f

www.rsc.org/advances

Ruthenium hydride/nitrogen tridentate ligand-catalyzed α-alkylation of acetamides with primary alcohols†

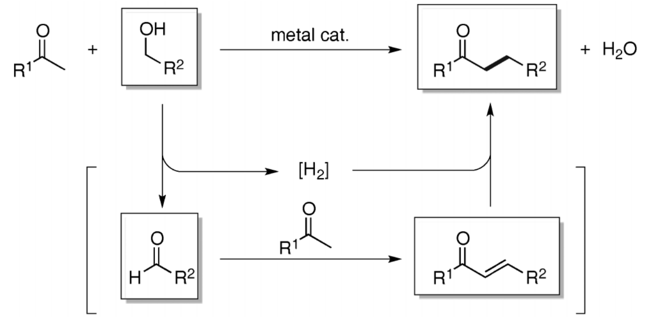
Takashi Kuwahara, Takahide Fukuyama and Ilhyong Ryu*

The α-alkylation reaction of acetamides with primary alcohols to afford the corresponding amides was accomplished effectively using $RuHCl(CO)(PPh_3)_3$ as a catalyst, nitrogen tridentate ligand L1 as an additive, and KO^tBu as a base. While the addition of bpy was effective only for benzylic alcohols, L1 affected the alkylation reaction when both benzylic and non-benzylic type alcohols were used.

In recent years, transition-metal-catalyzed α-alkylation reactions of carbonyl compounds using primary alcohols have attracted much attention in view of the atom-economy in which water is the only byproduct.[1] These transformations employ classical aldol reactions for the C–C bond-forming step, in which aldehydes are provided *via* the transfer dehydrogenation of primary alcohols by a metal catalyst and dehydrated aldol products act as dihydrogen acceptors from primary alcohols (Scheme 1). While the alkylation of methyl ketones,[2,3] acetic acid esters,[4] cyanoacetates,[5] malonates,[6] ketonitriles[7] and acetonitrile[8,9] has been attained, the alkylation of amides is only restricted to the specific amides, such as oxindoles[10] and 1,3-dimethyl barbituric acid.[11]

During the course of our study to explore the atom-economical reactions of alcohols based on the multitask ability of $RuHCl(CO)(PPh_3)_3$ as a catalyst,[12] we recently reported the $RuHCl(CO)(PPh_3)_3$-catalyzed α-alkylation reaction of ketones by primary alcohols,[3] in which we found that addition of a catalytic amount of 1,10-phenanthroline (Phen) dramatically accelerated the alkylation of ketones by nonbenzylic primary alcohols. In this work, we focused on the α-alkylation of acetamides using the same RuH complex as a catalyst, but with a combination of *N*,*N*-bidentate or *N*,*N*,*N*-tridentate ligands, such as 2,2′-bipyridine (bpy) or tridentate ligand **L1** (Fig. 1). Especially the tridentate ligand **L1** accelerated alkylation using both benzylic and non-benzylic alcohols. It should be noted that almost concurrently with this work, Huang and co-workers have reported similar α-alkylation of simple amides, in which they used an iridium pincer complex as a catalyst.[13]

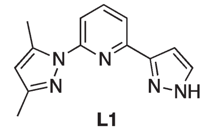
Using $RuHCl(CO)(PPh_3)_3$ as a catalyst, we initially investigated the reaction conditions using *N*,*N*-dimethylacetamide (**1a**) and benzyl alcohol (**2a**) as test substrates (Table 1). When 1.1 equiv. of **1a** was reacted with **2a** in the presence of 3 mol% of $RuHCl(CO)(PPh_3)_3$ and 1.3 equiv. of potassium *tert*-butoxide at 140 °C (bath temp) for 18 h in toluene (2 mL), the desired amide **3a** was obtained in 39% yield (entry 1). We examined some other bases, such as NaO^tBu (entry 2), Cs_2CO_3 (entry 3) and KOH (entry 4), but these bases were less effective or totally ineffective, unlike the case of ketone alkylation.[3] To encourage further the reaction using KO^tBu, we then tested several additives. The addition of 1,10-phenanthroline (Phen), which worked well for the acceleration of ketone α-alkylation, did not work in the present amide alkylation (entry 5). However, the addition of 10 mol% of 2,2′-bipyridine (bpy) resulted in a significant improvement in the yield of **3a** to 49% (entry 6). When **1a** was used in large excess without solvent, we obtained **3a** in 68% yield (entry 7). Inspired by the recent work of Yu and coworkers who found that Ru(II) complexes having a pyrazolyl-pyridyl-pyrazole ligand, **L1**, exhibited high catalytic activity in the transfer hydrogenation of ketones,[14] we examined the *N*,*N*,*N*-tridentate ligand, **L1** for the present



Scheme 1 General concept of metal-catalyzed α-alkylation of carbonyl compounds with alcohols.

Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan. E-mail: ryu@c.s.osakafu-u.ac.jp; Tel: +81 72 254 9695

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra42834f



L1

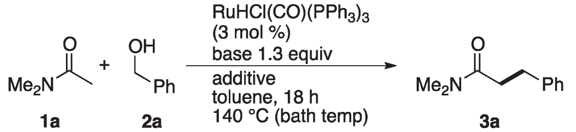
Fig. 1 Structure of **L1**.

α-alkylation of **1a**. Gratifyingly, the yield of **3a** was further improved to 76% (entry 8).

Using the reaction conditions of entry 7 (method A, bpy) and/or entry 8 (method B, **L1**), we then examined the generality of the α-alkylation of acetamides (Table 2). Using substituted benzyl alcohols **2a–g**, *N*,*N*-dimethyl-3-arylpropionamides **3a–g** were obtained in moderate to good yields (entries 1–7). The reaction of **1a** with 1-naphthalenemethanol (**2h**) gave the corresponding amides **3h** in 65% yield (entry 8). The alkylation of **1a** by furfuryl alcohol (**2i**) gave **3i** in modest yield (entry 9). The reaction of *N*-acetyl morpholine (**1b**) with **2a** in toluene gave the corresponding amide **3j** in 78% yield (entry 10). Compared to benzyl alcohols, non-benzylic type alcohols resulted in poorer yields when we used method A. However, when using method B, alkylation using hexanol (**2j**), cyclohexanemethanol (**2k**), and isoamyl alcohol (**2l**) gave the desired products **3k**, **3l**, and **3m** in good yields (entries 11–13).

Although the detailed mechanism has to wait further study, possible reaction mechanism is summarized in Scheme 2. An alkoxyruthenium complex **A** would be formed *in situ* from $RuHCl(CO)(PPh_3)_3$, **L1**, and an alcohol **2a**, which would then undergo β-hydride elimination to give a ruthenium hydride **B** and an aldehyde.[15] Base promoted aldol condensation of the resultant aldehyde with **1a** would give an α,β-unsaturated amide. Addition of the ruthenium hydride complex **B** to the α,β-unsaturated amide would afford a ruthenium enolate **C**, which would be protonated by an alcohol to give the α-alkylated amide **3** and the alkoxyruthenium **A**.

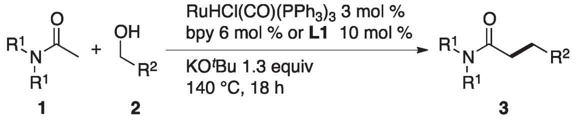
Table 1 Optimization of the reaction conditions[a]

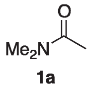
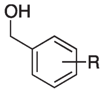
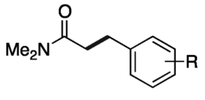
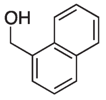
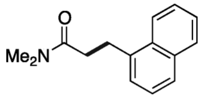
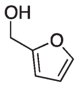
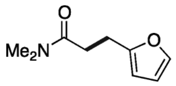
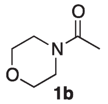
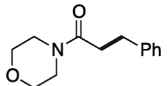
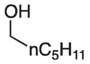
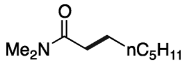
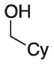
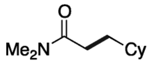
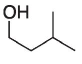
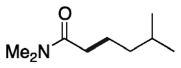


Entry	Base	Additive (mol %)	Yield (%)[b]
1	KO^{t}Bu	—	39
2	NaO^{t}Bu	—	10
3	Cs_2CO_3	—	0
4	KOH	—	0
5	KO^{t}Bu	Phen (10)	31
6	KO^{t}Bu	bpy (10)	49
7[c]	KO^{t}Bu	bpy (10)	68[d]
8[c]	KO^{t}Bu	**L1** (6)	76[d]

[a] Reaction conditions: **1a** (0.55 mmol), benzyl alcohol **2a** (0.50 mmol), $RuHCl(CO)(PPh_3)_3$ (3 mol%), base (1.3 equiv.), additive, toluene (2 mL), 140 °C for 18 h. [b] NMR yield. [c] **1a** was used as a solvent (2 mL). [d] Isolated yield.

Table 2 Ru-catalyzed α-alkylation of acetamides by primary alcohols[a]

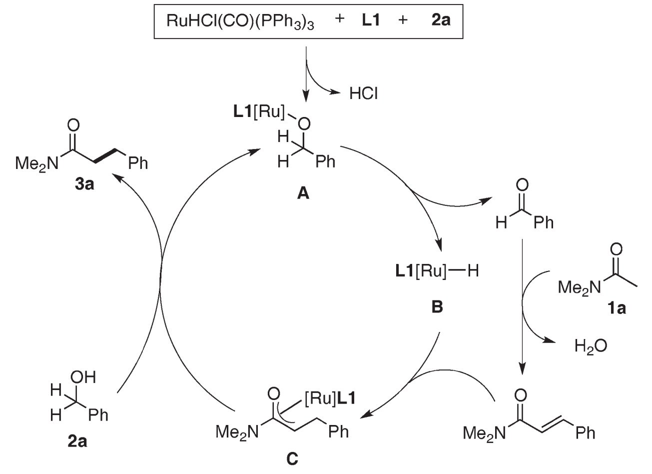


Entry	Amide 1	Alcohol 2	Method	Product 3	Yield (%)[b]
	 1a				
1		R = H **2a**	(B)	**3a**	76
2		*p*-^{t}Bu **2b**	(A)	**3b**	61
3		*p*-Ph **2c**	(A)	**3c**	89
4		*o*-OMe **2d**	(B)	**3d**	73
5		*m*-OMe **2e**	(B)	**3e**	76
6[c]		*p*-OMe **2f**	(A)	**3f**	70
7		*m*-CF_3 **2g**	(B)	**3g**	85
8	**1a**	 **2h**	(B)	 **3h**	65
9	**1a**	 **2i**	(B)	 **3i**	45
10[d]	 **1b**	**2a**	(A)	 **3j**	78
11	**1a**	 **2j**	(B)	 **3k**	76
12	**1a**	 **2k**	(B)	 **3l**	74
13	**1a**	 **2l**	(B)	 **3m**	61

[a] Method A: alcohol **2** (0.5 mmol), $RuHCl(CO)(PPh_3)_3$ (3 mol%), bpy (10 mol%), KO^{t}Bu (1.3 equiv.), **1a** (2 mL), 140 °C (bath temp), 18 h. Method B: **L1** (6 mol%) was used instead of bpy. [b] Isolated yield by silica gel chromatography. [c] 13 h. [d] Toluene solution (2 mL) of **1b** (1 mmol) was used.

In summary, we have found that the α-alkylation reaction of acetamides with primary alcohols can be successfully catalyzed by readily available $RuHCl(CO)(PPh_3)_3$ as a catalyst, KO^{t}Bu as a base, and tridentate amine **L1** as an ligand. A detailed mechanistic study and the applications using the ruthenium complexes having **L1** are currently underway in our laboratory.

This work was supported by a Grant-in-Aid for Scientific Research from MEXT and JSPS.



Scheme 2 Possible reaction mechanism.

Notes and references

1 For recent reviews, see: (*a*) G. Guillena, D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2007, **46**, 2358; (*b*) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555; (*c*) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753; (*d*) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (*e*) T. Suzuki, *Chem. Rev.*, 2011, **111**, 125; (*f*) Y. Obora and Y. Ishii, *Synlett*, 2011, 30.

2 (*a*) C. S. Cho, B. T. Kim, T.-J. Kim and S. C. Shim, *Tetrahedron Lett.*, 2002, **43**, 7987; (*b*) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi and Y. Ishii, *J. Am. Chem. Soc.*, 2004, **126**, 72; (*c*) C. S. Cho, *J. Mol. Catal. A Chem.*, 2005, **240**, 55; (*d*) R. Martínez, G. J. R. Brand, D. J. Ramón and M. Yus, *Tetrahedron Lett.*, 2005, **46**, 3683; (*e*) M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedrala and J. Park, *Angew. Chem., Int. Ed.*, 2005, **44**, 6913; (*f*) R. Martínez, D. J. Ramón and M. Yus, *Tetrahedron*, 2006, **62**, 8988; (*g*) Y. M. A. Yamada and Y. Uozumi, *Org. Lett.*, 2006, **8**, 1375; (*h*) Y. M. A. Yamada and Y. Uozumi, *Tetrahedron*, 2007, **63**, 8492; (*i*) F. Alonso, P. Riente and M. Yus, *Eur. J. Org. Chem.*, 2008, 4908; (*j*) K. Maeda, Y. Obora, S. Sakaguchi and Y. Ishii, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 689; (*k*) X. Cui, Y. Zhang, F. Shi and Y. Deng, *Chem.–Eur. J.*, 2011, **17**, 1021. For transition-metal-free alkylation, see: (*l*) Y.-F. Liang, X.-F. Zhou, S.-Y. Tang, Y.-B. Huang, Y.-S. Feng and H.-J. Xu, *RSC Adv.*, 2013, **3**, 7739.

3 T. Kuwahara, T. Fukuyama and I. Ryu, *Org. Lett.*, 2012, **14**, 4703.

4 Y. Iuchi, Y. Obora and Y. Ishii, *J. Am. Chem. Soc.*, 2010, **132**, 2536.

5 (*a*) M. Morita, Y. Obora and Y. Ishii, *Chem. Commun.*, 2007, 2850; (*b*) R. Grigg, C. Löftberg, S. Whitney, V. Sridharan, A. Keep and A. Derrick, *Tetrahedron*, 2009, **65**, 849.

6 (*a*) S. J. Pridmore and J. M. J. Williams, *Tetrahedron Lett.*, 2008, **49**, 7413; (*b*) A. Corma, T. Ródenas and M. J. Sabater, *J. Catal.*, 2011, **279**, 319.

7 P. A. Slatford, M. K. Whittlesey and J. M. J. Williams, *Tetrahedron Lett.*, 2006, **47**, 6787.

8 (*a*) B. Anxionnat, D. G. Pardo, G. Ricci and J. Cossy, *Org. Lett.*, 2011, **13**, 4084; (*b*) T. Sawaguchi and Y. Obora, *Chem. Lett.*, 2011, **40**, 1055.

9 T. Kuwahara, T. Fukuyama and I. Ryu, *Chem. Lett.*, DOI: 10.1246/cl.130465.

10 (*a*) T. Jensen and R. Madsen, *J. Org. Chem.*, 2009, **74**, 3990; (*b*) R. Grigg, S. Whitney, V. Sridharan, A. Keep and A. Derrick, *Tetrahedron*, 2009, **65**, 4375.

11 C. Löfberg, R. Grigg, A. Keep, A. Derrick, V. Sridharan and C. Kilner, *Chem. Commun.*, 2006, 5000.

12 (*a*) T. Doi, T. Fukuyama, J. Horiguchi, T. Okamura and I. Ryu, *Synlett*, 2006, 721; (*b*) T. Doi, T. Fukuyama, S. Minamino and I. Ryu, *Synlett*, 2006, 3013; (*c*) T. Doi, T. Fukuyama, S. Minamino, G. Husson and I. Ryu, *Chem. Commun.*, 2006, 1875; (*d*) T. Fukuyama, T. Doi, S. Minamino, S. Omura and I. Ryu, *Angew. Chem., Int. Ed.*, 2007, **46**, 5559; (*e*) S. Omura, T. Fukuyama, J. Horiguchi, Y. Murakami and I. Ryu, *J. Am. Chem. Soc.*, 2008, **130**, 14094; (*f*) S. Omura, T. Fukuyama, Y. Murakami, H. Okamoto and I. Ryu, *Chem. Commun.*, 2009, 6741; (*g*) A. Denichoux, T. Fukuyama, T. Doi, J. Horiguchi and I. Ryu, *Org. Lett.*, 2010, **12**, 1; (*h*) T. Fukuyama, H. Okamoto and I. Ryu, *Chem. Lett.*, 2011, **40**, 1453.

13 In the preparation of this manuscript, it was reported that iridium complex can catalyzed α-alkylation of amides, see: L. Guo, Y. Liu, W. Yao, X. Leng and Z. Huang, *Org. Lett.*, 2013, **15**, 1144.

14 W. Jin, L. Wang and Z. Yu, *Organometallics*, 2012, **31**, 5664.

15 Treatment of RuHCl(CO)(PPh$_3$)$_3$ and **L1** in CH$_2$Cl$_2$ gave a Ru complex bearing two PPh$_3$, one **L1**, CO and hydride (by NMR). While the structure of the complex has yet to be fully characterized, we confirmed that the **L1**-Ru shows a catalytic activity for the present α-alkylation of amides.