ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Y. Zheng, X. Nie, Y. Long, L. Ji, H. Fu, X. Zheng, H. Chen and R. Li, *Chem. Commun.*, 2019, DOI: 10.1039/C9CC06339K.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C9CC06339K

COMMUNICATION

Ruthenium-Catalyzed Synthesis of *N*-substituted Lactams by Acceptorless Dehydrogenative Coupling of Diols with Primary Amines

Received 00th January 20xx,
Accepted 00th January 20xx

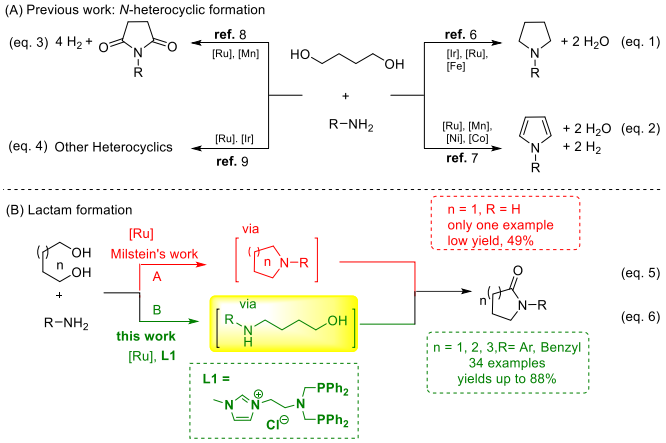
DOI: 10.1039/x0xx00000x

Yanling Zheng, Xufeng Nie, Yang Long, Li Ji, Haiyan Fu*, Xueli Zheng, Hua Chen and Ruixiang Li *[a]

Herein, we report the first example of synthesis *N*-substituted lactams via an acceptorless dehydrogenation coupling of diols with primary amines in one step, which was enabled by combining $Ru_3(CO)_{12}$ with a hybrid N-heterocyclic carbene-phosphine-phosphine ligand as the catalyst.

The *N*-substituted lactam scaffold is an important template due to its frequent occurrence in bioactive and pharmaceutically molecules, agrochemicals and functional materials.[1] Typically, the preparation of *N*-substituted lactam relies on cyclization by amide formation between a toxic or corrosive carboxylic acid, acid chloride or anhydride with an amine,[2] and other C-N coupling of lactams methodologies were successively reported.[3] However, most of these protocols suffer from various drawbacks, including the addition of stoichiometric amounts of inorganic oxidants, multistep synthetic operations, and the generation of copious hazardous waste. In recent years, the acceptorless dehydrogenative coupling (ADC) between alcohols and amines has attracted significant interest and has been used for the synthesis of a number of amides[4] and C-N bond forming reactions.[5] ADC reactions are green and environmentally friendly because of the avoidance of using redundant sacrificial hydrogen acceptors. Such reaction generally only release environmentally-friendly hydrogen (a clean and efficient fuel) and/or water as the byproducts.

From the point of view of retrosynthetic analysis, *N*-substituted lactams can be prepared from diols and amines via the formation of both C-N and amide bonds. According to reports, the ADC reactions between diols and primary amines are commonly employed for the construction of *N*-containing heterocycles (Scheme 1A), such as pyrrolidines (eq. 1),[6] pyrroles (eq. 2),[7] cyclic imides (eq. 3)[8] and quinolines or indoles (eq. 4).[9] However, the preparation of *N*-substituted lactams from diols and amines has not been fully explored. Such a transformation requires that two hydroxyl groups selectively undergo two different dehydrogenation processes: *N*-alkylation and amidation, which poses a significant challenge. So far, only one example of the formation of γ-lactam from 1,4-butanediol and aqueous ammonia via a dehydrogenation process has been demonstrated by Milstein et al.[10] The reaction proceeds via pyrrolidine intermediate (route A), giving the desired product with a low yield of 49% (Scheme 1B, eq. 5). Unfortunately, the conversion of *N*-substituted pyrrolidines to the *N*-substituted lactams via route A is proved to be difficult. Alternatively, the transformation of diols and primary amines to lactams can also be achieved via the amino alcohol intermediates, which contain both a secondary amine moiety and a hydroxyl group (route B) (eq. 6). Indeed, a number of catalytic systems have been reported for the cyclic amidation of amino alcohols.[11]



Scheme 1 Metal-catalyzed synthesis of N-heterocycles via dehydrogenation of 1,4-diols with amines.

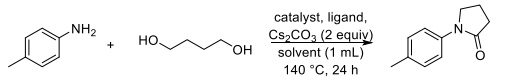
Recently, our group has developed a hybrid *N*-heterocyclic carbene (NHC)−phosphine−phosphine ligand **L1**. Owing to both the anchoring effect of its NHC moiety and hemilability of phosphine group, as well as the preference of facial type

[a]*Key Laboratory of Green Chemistry & Technology, Ministry of Education College of Chemistry, Sichuan University, 29 Wangjiang Road, Chengdu 610064, P. R. China. E-mail: scufhy@scu.edu.cn (H. F.); liruixiang@scu.edu.cn (R. L.)*

† Electronic supplementary information (ESI) available: Experimental procedures, Fig. S1, Fig. S2, characterization data, and copies of NMR spectra. See DOI: 10.1039/x0xx00000x

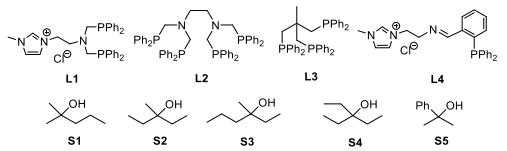
coordination, **L1** has exhibited good performance in several Ru-catalyzed dehydrogenation reactions.[12] More importantly, a selective *N*-alkylation of primary amines with alcohols to secondary amines has been developed based on a **L1/**Ru system.[13] In continuation of our investigations on the properties of ligand **L1**, we herein demonstrate that using **L1** / $[Ru_3(CO)_{12}]$ as catalyst enables the selective transformation of diols and primary amines to *N*-substituted lactam (Scheme 1B). To the best of our knowledge, this represents the first example of the direct synthesis of *N*-substituted lactams from diols and primary amines via an ADC reaction.

Table 1 Optimization of reaction conditions.[a]



1a 2a 3aa

Entry	Catalyst	Ligand	Solvent	Yield %[b]
1	$Ru(COD)Cl_2$	**L1**	Toluene	26
2	$Ru_3(CO)_{12}$	**L1**	Toluene	31
3	$RuHCl(CO)(PPh_3)_3$	**L1**	Toluene	4[c]
4	$Ru(C_6H_6)_2Cl_2$	**L1**	Toluene	22
5	$Ru_3(CO)_{12}$	**L2**	Toluene	0
6	$Ru_3(CO)_{12}$	**L3**	Toluene	18
7	$Ru_3(CO)_{12}$	**L4**	Toluene	12
8	$Ru_3(CO)_{12}$	**L1**	*t*-BuOH	38
9	$Ru_3(CO)_{12}$	**L1**	*t*-Amyl-OH	40
10	$Ru_3(CO)_{12}$	**L1**	**S1**	43
11	$Ru_3(CO)_{12}$	**L1**	**S2**	63
12	$Ru_3(CO)_{12}$	**L1**	**S3**	81 (85)[c]
13	$Ru_3(CO)_{12}$	**L1**	**S4**	27
14	$Ru_3(CO)_{12}$	**L1**	**S5**	trace
15	-	**L1**	**S3**	0
16	$Ru_3(CO)_{12}$	-	**S3**	0

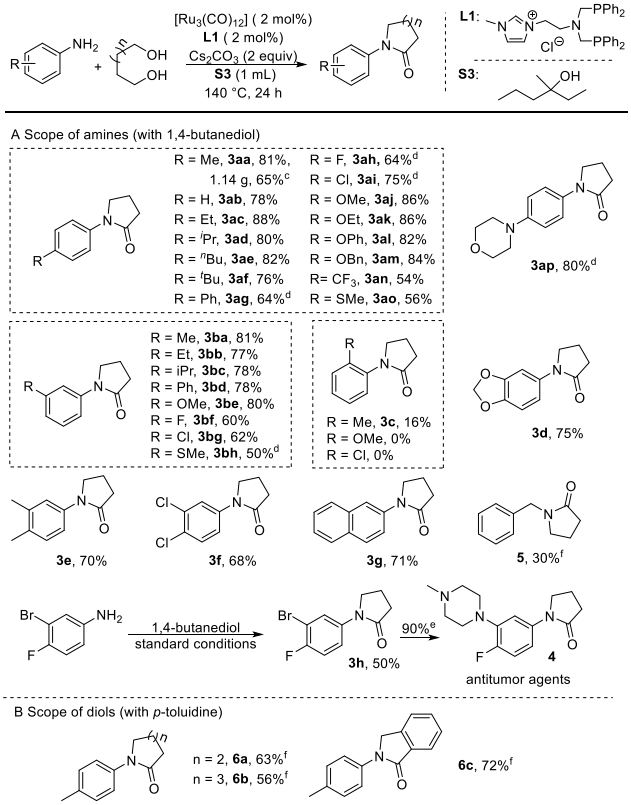


[a]Unless otherwise noted, the reaction was carried out under open condition to nitrogen with **1a** (0.25 mmol), **2a** (0.5 mmol), catalyst (2 mol%), ligand (2 mol%), Cs_2CO_3 (0.5 mmol) in solvent (1 mL) at 140 °C for 24 h. [b]Isolated yield. [c]NMR yield using pyrazine as the internal standard.

Initially, the acceptorless dehydrogenative coupling of *p*-toluidine **1a** (0.25mmol) and 1,4-butanediol **2a** (0.5 mmol) was chosen as a model reaction. A variety of ruthenium salts (2 mol%) were evaluated as the catalyst precursor in the presence of the ligand **L1** (2 mol%) and Cs_2CO_3 (2 equiv) in toluene (1 mL) at 140°C (Table 1, entries 1-4). To our delight, the desired product *N*-(4-methylphenyl)-2-pyrrolidinone **3aa** was obtained in 4-31% yields, illustrating the feasibility of the Ru/**L1** ADC system for the preparation of *N*-substituted lactams. In addition, using other ligands instead of **L1** in combination with the best catalyst precursor, $Ru_3(CO)_{12}$, led to a significant decline in yield, and even complete inhibition of the reaction (entries 5-7), which further highlighted the unique catalytic properties of **L1** in this transformation. Considering the poor solubility of 1,4-butanediol in toluene, we anticipated that the use of alcohol solvent would help resolve the diols and facilitate the reaction. Hence, tertiary alcohols, which didn't possess an α-H, were used to avoid dehydrogenation occurring on solvent. After a brief screen (entries 8-14), the commercially available tertiary alcohol 3-methyl-3-hexanol (**S3**) was found to be the optimal solvent, which significantly increased the reaction efficiency and allowed for the synthesis of **3aa** in 81% isolated yield (entry 12). Note that no desired product was observed in the absence of catalyst or ligand (entries 15-16).

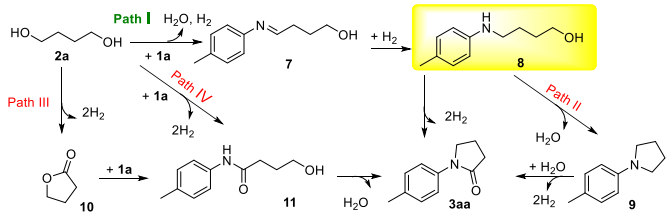
With the optimized conditions in hand, the generality of the reaction was investigated. Firstly, we examined the amine scope. As shown in Scheme 2A, different substituents at the *para* position of aniline were explored and the nature of substituents appeared to have little effect on product yield. Various linear and branched alkyl groups were tolerated, affording the corresponding products in approximately 80% yield (**3aa**-**3af**). A gram scaled-up reaction was also carried out, giving 3aa in 65%, which indicated its feasibility on a more synthetically useful amount. A substrate bearing phenyl group also gave its corresponding product in a desirable yield (**3ag**). The substrates bearing halogen groups, including F and Cl, were also converted to the desired products in moderate yield (**3ah-3ai**).

Scheme 2 Scope of substrates.[a,b]



[a]Unless otherwise noted, the reaction was run on a 0.25 mmol scale under the standard conditions depicted in Table 1. [b]Isolated yields. [c]The reaction was run on a 10 mmol scale. [d]48h. [e]Reaction conditions: 1-methylpiperazine, $Pd(dba)_2$, xantphos, NaO^tBu, toluene, 110 °C, air. [f]4 equiv Cs_2CO_3

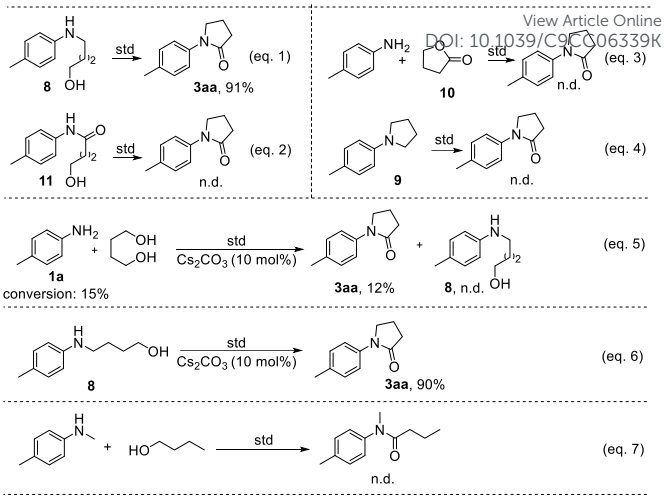
Alkoxy and aryloxy groups also proved to be compatible with this system (**3aj**-**3am**). Substrates bearing an electron-withdrawing trifluoromethyl group (**3an**), and thiomethyl group (**3ao**), a strong nucleophile that might competitively coordinate to the ruthenium catalyst, also underwent reaction smoothly, affording the desired products in moderate yields. Gratifyingly, the pharmaceutical scaffold morpholine could also be efficiently introduced in this system (**3ap**). Furthermore, a range of *m*-substituted anilines also showed considerable reactivity, providing the corresponding *N*-substituted γ-lactams in moderate to high yields (**3ba-3bh**). As steric hindrance greatly affected the reaction efficiency, the conversions of anilines bearing substituents at the *ortho* position were poor, with only *o*-toluidine being converted to 1-(*o*-tolyl)pyrrolidin-2-one in 16% yield (**3c**). Remarkably, di-substituted anilines smoothly delivered the corresponding lactams in moderate yields (**3d-3g**). Notably, the remaining Br atom in 1-(3-bromo-4-fluorophenyl)pyrrolidin-2-one (**3h**) allowed it to be further converted into **4** via a cross-coupling reaction to give an antitumor agent. More importantly, benzylamine, an aliphatic amine, which generally takes part in a competitive dehydrogenation process to give the corresponding imine and nitrile,[14] could also be employed to give its corresponding product albeit with a lower yield (**5**) (detailed results see SI). Subsequently, the scope of the diols was examined as shown in Scheme 2B. The conversion of 1,5-pentanediol and 1,6-hexanediol gave six- and seven-membered lactams in yields of 63% and 56%, respectively (**6a, 6b**); phthaldyl alcohol was also amenable to the reaction conditions, affording *N*-substituted isoindolinone **6c** in 72% yield.



Scheme 3 Possible reaction pathways.

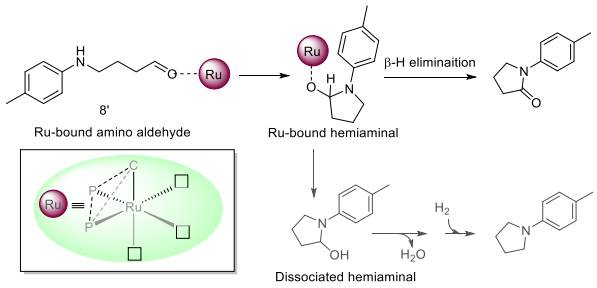
Based on the existing metal-catalyzed acceptorless dehydrogenative coupling works,[15] the reaction might proceed via amino alcohol **8** (Path I), pyrrolidine **9** (Path II), lactone **10** (Path III), or hydroxyamide **11** (Path IV) intermediates (Scheme 3). We subsequently synthesized these four intermediates and evaluated their reactivity under the standard conditions (Scheme 4). The desired product was not detected when pyrrolidine **9**, lactone **10**, or hydroxyamide **11** were used, thus ruling out the pathways II-IV (eqs. 2-4). In contrast, the intermediate amino alcohol **8** gave the product **3aa** in a high yield of 91% (eq. 1), indicating that the reaction most likely proceeds via Pathway I. Monitoring the reaction with GC-MS (Fig. S1), we found that with the consumption of the amine **1a**, imine **7** was produced and rapidly transformed to amino alcohol **8**, which underwent cyclic amidation to give the desired product; these results provided strong evidences for pathway I.

Two additional experiments, using **8** as substrate and reacting *p*-toluidine **1a** with 1,4-butanediol, were performed in a catalytic amount of base, respectively. The reaction between



Scheme 4 Studies on the reaction pathway.

1a and 1,4-butanediol gave **3aa** in the low yield of 12%, without any amino alcohol **8** being detected (eq. 5). On the contrary, the amino alcohol **8** was transformed into **3aa** in the high yield of 90% (eq. 6). It is worth mentioning that for the steric bulky anilines and secondary amines, only a few existing Ru-based catalysts were compatibility and all showed the low reactivity.[11] To the best of our knowledge, this is the first catalytic system with such high reactivity regarding the *N*-phenyl lactam formation from the corresponding amino alcohol. By contrast, the intermolecular amidation between *N*-methyl toluidine and butanol in this system failed to give any amide product (eq. 7), indicating that intramolecular nucleophilic addition occurred on the Ru-bound amino aldehyde is more favourable than the intermolecular fashion. The Ru-bound aminal-aldehyde likely pre-organizes as a cyclic conformer to facilitate cyclic lactam formation.



Scheme 5 Plausible mechanism.

On the basis of these experimental results, we suggested that, under Ru-**L1** catalysis, the reaction initially proceeds with *N*-alkylation between the primary amine and diol in the presence of 2.0 equiv Cs_2CO_3 to afford the intermediate amino alcohol **8**. Then, the amino alcohol undergoes dehydrogenation to a Ru-bound amino aldehyde **8'** in a half-closed cyclic conformer, followed by formation of a Ru-bound hemiaminal, which is subsequently dehydrogenated to the corresponding lactam via a β-H elimination (Scheme 5). In order to form amide, the cyclic hemiaminal must remain in a Ru-bound state,[4e]

otherwise, the free hemiaminal would be dehydrated and followed by hydrogenation to tertial amine.

Our system shows an exceedingly high selectivity towards the formation of *N*-substituted lactams, with only a trace amount of *N*-substituted pyrrolidine. The unique selectivity of Ru-**L1** catalytic system towards lactam formation probably benefits from the supporting ligand **L1**, which brings several advantages to the system: Firstly, the facial configuration of *in-situ* formed Ru-**L1** complex provides a relatively wide coordination space around Ru,[12] thus allowing for accommodation of the substrates and ligands as geometrically required. Especially, it may be capable of containing an aminal alcohol as a ligand around the Ru-bound hemiaminal to enhance its dehydrogenation to amide. It has been demonstrated by Crabtree that incorporating a ligand with N-H protons into the catalyst greatly accelerates amide formation from the hemiaminal;[4d,4e] Secondly, the hemilability of the phosphine moiety could promote both substrate binding, and more importantly, it would provide the coordination site for *cis* β-H elimination; Thirdly, the anchoring effect of the NHC moiety can stabilize the catalytically active species at high temperature, which is required for the β-H elimination.[4e] Furthermore, its strong σ-donating ability also plays an important role in facilitating the dehydrogenation of hemiaminal to amide over the elimination of water,[11b] and the low product yield with tripodal triphosphine **L3** (entry 6 in Table 1), which has a similar chelating model with **L1** without NHC moiety, further supports that.

In conclusion, we have developed the first Ru-catalyzed synthesis of *N*-substituted lactams from diols and amines in one step. The reaction is environmentally benign, with H_2 and water as only byproducts. A careful study on the reaction mechanism reveals that the acceptorless dehydrogenation of diols might involve successive *N*-alkylation and amidation processes to give the desired products. Further investigations regarding the reaction mechanism are ongoing.

We thank the National Natural Science Foundation of China (21572137 and 21871187) and the Key Program of Sichuan Science and Technology Project (nos. 2018GZ0312, 2019YFG0146) for financial support. We also acknowledge Comprehensive Training Platform of Specialized Laboratory, College of Chemistry, Sichuan University, for HRMS analysis.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) J. S. Sajko, V. L. Bilić, I. Kosalec and I. Jerić, *ACS Comb. Sci*., 2019, **21**, 28; (b) L.-W. Ye, C. Shu and F. Gagosz, *Org. Bimol. Chem.*, 2014, **12**, 1833.

2 D. Astill and V. Boekelheide, *J. Am. Chem. Soc.*, 1955, **77**, 4079.

3 (a) J. P. Michael, C. B. D. Koning and T. V. Stanbury, *Tetrahedron Lett.*, 1996, **37**, 9403; (b) J. P. Michael, C. B. D. koning, G. D. Hosken and T. V. Stanbury, *Tetrahedron*, 2001, **57**, 9635; (c) A. Millet, Q. Lefebvre and M. Rueping, *Chem. Eur. J.*, 2016, **22**, 13464; (d) Y. He, Z. Zheng, Y. Liu, J. Qiao, X. Zhang and X. Fan, *Org. Lett.*, 2019, **21**, 1676; (e) W. Guo, J. E. Gómez, L. M.-Rodríguez, N. A. G. Bandeira, C. Bo and A. W. Kleij, *ChemSusChem*, 2017, **10**, 1969; (f) M. Rauser, R. Eckert, M. Gerbershagen and M. Niggemann, *Angew. Chem. Int. Ed.*, 2019, **58**, 6713.

4 (a) P. Daw, A. Kumar, N. A. E.-Jalapa, Y. B.-David, and D. Milstein, *J. Am. Chem. Soc.,* 2019, **141**, 12202; (b) L. U. Nordstrøm, H. Vogt, and R. Madsen, *J. Am. Chem. Soc.,* 2008, **130,** 17672; (c) C. Chen, Y. Zhang, and S. H. Hong, *J. Org. Chem*., 2011, **76**, 10005; (d) N. D. Schley, G. E. Dobereiner, and R. H. Crabtree, *Organometallics*, 2011, **30**, 4174; (e) A. Nova, D. Balcells, N. D. Schley, G. E. Dobereiner, R. H. Carbtree, and O. Eisenstein, *Organometallics*, 2010, **29**, 6548; (f) A. Prades, E. Peris, and M. Albrecht, Organometallics, 2011, **30**, 1162.

5 (a) B. Blank, S. Michik, R. Kempe, *Chem. Eur. J*., 2009, **15**, 3790; (b) L. M. Broomfield, Y. Wu, E. Martin, A. Shafir, *Adv. Synth. Catal*.,2015, **357**,3538; (c) S. Michik, R. Kempe, *Chem. Eur. J.*, 2010,**16**, 13193.

6 (a) W. Zhang, X. Dong and W. Zhao, *Org. Lett.*, 2011, **13**, 5386; (b) A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *J. Org. Chem.*, 2011, **76**, 2328; (c) A. Afanasenko, S. Elangovan, M. C. A. Stuart, G. Bonura, F. Frusteri and K. Barta, *Catal. Sci. Technol.*, 2018, **8**, 5498; (d) X. Cui, X. Dai, Y. Deng and F. Shi, *Chem. Eur. J.*, 2013, **19**, 3665.

7 (a) J. C. Borghs, Y. Lebedev, M. Rueping and O. El-Sepelgy, *Org. Lett.*, 2019, **21**, 70; (b) K. Singh, K. M. Kabadwal, S. Bera, A. Alanthadka and D. Banerjee, *J. Org. Chem.*, 2018, **83**, 15406; (c) N. D. Scheley, G. E. Dobereiner and R. H. Crabtree, *Organometallics*, 2011, **30**, 4174; (d) P. Daw, Y. B.-David and D. Milstein, *J. Am. Chem. Soc.*, 2018, **140**, 11931.

8 (a) N. A. E.-Jalapa, A. Kumar, G. Leitus, Y. D.-Posner and D. Milstein, *J. Am. Chem. Soc.*, 2017, **139**, 11722; (b) A. Kumar, T. Janes, N. A. E.-Jalapa and D. Milstein, *J. Am. Chem. Soc.*, 2018, **140**, 7453; (c) J. Zhang, M. Senthilkumar, S. C. Ghosh and S. H. Hong, *Angew. Chem. Int. Ed.*, 2010, **49**, 6391.

9 (a) A. Nandakumar, S. P. Midya, V. G. Landge and E. Balaraman, *Angew. Chem. Int. Ed.*, 2015, **54**, 11022; (b) P. J. L.-Campaner, R. B.-Garrido, R. Ballesteros and B. Abarca, *J. Org. Chem.*, 2018, **83**, 521.

10 (a) J. R. Khusnutdinova, Y. B.-David, and D. Milstein, *J. Am. Chem. Soc*., 2014, **136**, 2998; (b) U. Gellrich, J. R. Khusnutdinova, G. M. Leitus, and D. Milstein, *J. Am. Chem. Soc*., 2015, **137**, 4851.

11 (a) J. H. Dam, G. Osztrovszky, L. U. Nordstom, and R. Madsen, *Chem. Eur. J.*, 2010, **16**, 6820; (b) Y. Zhang, C. Chen, S. C. Ghosh, Y.-X. Li, and S. H. Hong, *Organometallics* 2010, **29**, 1374; (c) M. Trincado, K. Kühlein, and H. Grützmacher, *Chem. Eur. J*., 2011, **17**, 11905; (d) S. Herter, S. M. Mckenna, A. R. Frazer, and S. Leimkühler, *ChemCatChem,* 2015, **7**, 2313; (e) L. Huang, G. V. Sayoga, F. Hollmann, and S. Kara, *ACS Catal*., 2018, **8**, 8680.

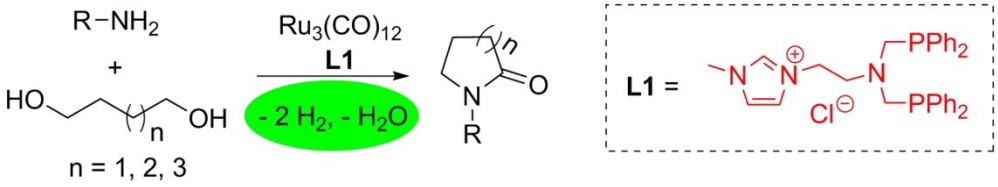
12 H.-M. Liu, L. Jian, C. Li, C.-C Zhang, H.-Y. Fu, X.-L. Zheng, H. Chen, and R.-X. Li, *J. Org. Chem.*, 2019, **84**, 9151.

13 X.-J. Yu, H.-Y. He, L. Yang, H.-Y. Fu, X.-L. Zheng, H. Chen, R.-X. Li, *Catal. Commun.,* 2017, **95**, 54.

14 (a) M. Varyani, P. K. Khatri, S. L. Jain, *Tetrahedron Lett*., 2016, **57**, 723; (b) J. W. Kim, K. Yamaguchi, and N. Mizuno, *Angew. Chem. Int. Ed*., 2008, **47**, 9249; (c) R. Ray, S. Chandra, V. Yadav, P. Mondal, D. Maiti, and G. K. Lahiri, *Chem. Commun.*, 2017, **53**, 4006.

15 (a) C. Gunanathan, Y. B.-David and D. Milstein, *Science*, 2007, **317**, 790; (b) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555; (c) C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 1229712.

View Article Online
DOI: 10.1039/C9CC06339K



- *First example of Ru-catalyzed dehydrogenation of diols to N-substituted lactams*
- *Over 30 examples*
- *Yields up to 88%*
- *Unprecedented selectivity*

134x41mm (300 x 300 DPI)