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Highly Efficient Ruthenium-Catalyzed Oxime to Amide Rearrangement

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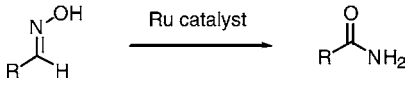
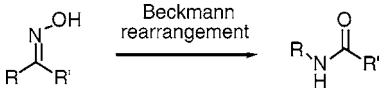
ABSTRACT



A wide range of aldoximes has been converted into the corresponding amides using the ruthenium-based catalyst $Ru(PPh_3)_3(CO)H_2$/dppe/TsOH. The amides are generated in high yield and selectivity, with catalyst loading as low as 0.04 mol %.

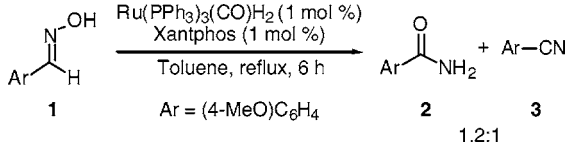
The Beckmann rearrangement of oximes into amides is a well-known reaction involving the migration of a group from carbon to nitrogen (Scheme 1).[1] It is typically performed using strong acid, PCl_5, or other activating agents. While the migrating group can be alkyl or aryl, it is rarely hydrogen that migrates, and so the Beckmann rearrangement is not a general process for the conversion of aldoximes into primary amides.[2]

Scheme 1. Beckmann Rearrangement of Oximes



The rearrangement of aldoximes into amides has been reported using nickel,[3] palladium (poor selectivity),[4] and rhodium catalysts,[5] as well as our own recent report of iridium catalysts for this reaction.[6] However, all of these reactions require relatively high catalyst loadings or forcing temperatures, and we therefore wished to identify a more efficient catalyst for this process. While ruthenium catalysts are known to catalyze the dehydration of aldoximes into nitriles,[7] they have not previously been used for the selective formation of amides. We have recently reported the use of $Ru(PPh_3)_3(CO)H_2$ in combination with the bidentate ligand Xantphos[8] for the formation of C−C bonds from alcohols[9] and chose this as a starting point for this investigation. Treatment of oxime **1** with $Ru(PPh_3)_3(CO)H_2$ (1 mol %) and Xantphos (1 mol %) in toluene at reflux for 6 h led to the formation of the amide **2** and nitrile **3** in a 1.2:1 ratio (Scheme 2).

Scheme 2. Formation of Amide and Nitrile from Oxime



1 Ar = (4-MeO)C_6H_4 **2** **3** 1.2:1

The use of alternative bidentate phosphines had a significant effect on the ratio of amide to nitrile products, as seen in Table 1.

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(2) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001; p 1415 and references therein.
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(8) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.
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Table 1. Effect of Bidentate Ligand on Selectivity

diphosphine	conversion[a] (%)	amide **2**	nitrile **3**	selectivity
none	44	23	21	1.1:1
Xantphos	49	27	22	1.2:1
DPEphos	55	31	24	1.3:1
(*R*)-Phanephos[10]	56	40	16	2.5:1
(*R*)-BINAP	53	34	19	1.8:1
(*R*)-Synphos[11]	48	33	15	2.2:1
(*R*)-Me-Duphos[12]	43	33	10	3.3:1
dppF	42	29	13	2.2:1
dippF[13]	38	16	22	0.7:1
dppp	53	45	8	5.6:1
dppe	47	41	6	6.8:1

[a] Conditions: oxime (1.0 mmol), $Ru(PPh_3)_3(CO)H_2$ (1 mol %), diphosphine (1 mol %), PhMe (2 cm^3), 111 °C, 2 h.

From the results in Table 1, the use of dppe as the bidentate ligand was chosen for further optimization, as detailed in Table 2. The use of alternative solvents afforded no benefits,

Table 2. Optimization of Amide Formation

additive	conversion[a] (%)	amide **2**	nitrile **3**	selectivity
none	47	41	6	6.8:1
Cs_2CO_3	61	53	8	6.6:1
$LiOH·H_2O$	64	56	8	7:1
^tBuOK[b]	65	58	7	8.3:1
$C_2H_5CO_2H$	46	41	5	8.2:1
Ac_2O	32	27	5	5.4:1
p-$TsOH·H_2O$	73	70	3	23.3:1

[a] Conditions: oxime (1.0 mmol), additive (1 mol %), $Ru(PPh_3)_3(CO)H_2$ (1 mol %), dppe (1 mol %), PhMe (2 cm^3), 111 °C, 2 h. [b] 2 mol %.

while the addition of base made a small improvement to the conversion but had little effect on selectivity. However, the addition of *p*-toluenesulfonic acid had a beneficial effect on conversion and selectivity.

Further optimization of the reaction conditions by varying the ratio of catalyst to *p*-toluenesulfonic acid, along with catalyst loading, was performed (Table 3). The use of 4 equiv

Table 3. Optimization of Amide Formation

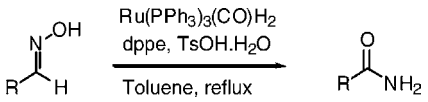
Ru (mol %)	*p*-TsOH (mol %)	conversion[a] (%)	amide **2**	nitrile **3**	selectivity
1	1	100	97.3	2.7	36:1
0.5	0.5	72.5	70	2.5	28:1
0.5	1	87.5	85.5	2.0	43:1
0.5	2	100	97.7	2.3	43:1
0.2	0.8	100	97.9	2.1	47:1
0.1	0.4	100[b]	98.5	1.5	66:1

[a] Conditions: oxime (5 mmol), dppe (1 equiv with respect to Ru), PhMe (5 cm^3), 111 °C, 2 h. [b] 6 h.

of *p*-toluenesulfonic acid with respect to the ruthenium complex provided very high levels of selectivity in favor of the amide **2**. The addition of acid CF_3CO_2H to ruthenium hydride complexes of the type L_nRuH_2 has been shown by Jung and Garrou to lead to the formation of $L_nRu(O_2CCF_3)_2$ (via metathesis).[14]

With an efficient catalyst in hand, we examined a range of oximes in the catalytic rearrangement reaction. Table 4

Table 4. Rearrangement of Oximes into Amides[a]



entry	R	catalyst (mol %)	time (h)	yield[b] (%)
1	(*Z*)-C_6H_5	0.1	8	92
2	(*E*)-C_6H_5	0.1	8	94
3	(4-MeO)C_6H_4	0.1	8	93
4	(4-NO_2)C_6H_4	0.2	4	94
5	(2-NO_2)C_6H_4	0.5	6	82
6	(4-CF_3O)C_6H_4	0.2	6	95
7	(2,4-Cl)C_6H_3	0.2	6	88
8[c]	2-furyl	0.2	6	80
9	(2-OH)C_6H_4	1.0	6	85
10	$C_6H_5CH{=}CH$	0.2	4	90
11	C_3H_7	0.1	8	91
12	C_7H_{15}	0.1	8	87

[a] Conditions: alcohol (5.0 mmol), 1:1:4 ratio of Ru/dppe/$TsOH·H_2O$, PhMe (5 mL), 111 °C. [b] Isolated yields after recrystallization or column chromatography. [c] 1,4-Dioxane used as solvent.

illustrates various oximes that were readily rearranged into the corresponding amides. The (*E*)- and (*Z*)-oximes (entries 1 and 2) gave similar results, and electron-donating (entry 3) and electron-withdrawing (entry 4) groups are tolerated, even at low catalyst loadings. The furyl oxime (entry 8) was insoluble in toluene, but the reaction was successful when 1,4-dioxane was used as the solvent. The presence of an *o*-hydroxy group (entry 9) slowed the reaction, and we assume that this substrate hinders catalysis by acting as a bidentate substrate. Nevertheless, the reaction could be run to completion with a higher catalyst loading (1.0 mol %). Unsaturated (entry 10) and aliphatic (entries 11 and 12) oximes were also readily isomerized into the corresponding amides with good isolated yields. In most cases, the presence of small (>3%) amounts of nitrile was identified from the ^1H NMR spectra of the crude material, but crystallization of the products readily afforded pure amide.

With catalyst loadings of between 0.1 and 1.0 mol % for the entries in Table 4, we were interested to see whether even lower catalyst loading could be used in a favorable case.

(10) (*R*)-Phanephos = (*S*)-(+)-4,12-bis(diphenylphosphino)[2,2]paracyclophane. Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207.

(11) (*R*)-Synphos = (*R*)-(+)-6,6′-bis(diphenylphosphino)-2,2′,3,3′-tetrahydro-5,5′-bi-1,4-benzodioxin. Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931.

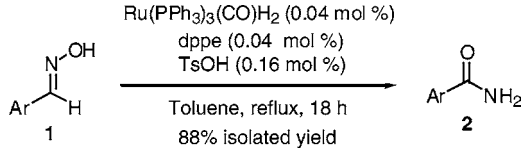
(12) (*R*)-Me-Duphos = (−)-1,2-bis(2*R*,5*R*)-2,5-dimethylphospholano)-benzene. Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518.

(13) DippF = 1,1′-bis(diisopropylphosphino)ferrocene.

(14) Jung, C. W.; Garrou, P. E. *Organometallics* **1982**, *1*, 658.

We chose to examine the reaction of oxime **1** with a catalyst loading of 0.04 mol % and were pleased to find that the reaction was complete after 18 h and the product **2** was isolated in 88% yield (Scheme 3). The reaction was

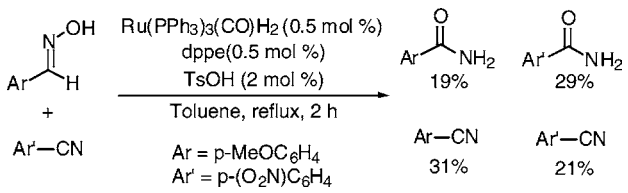
Scheme 3. Use of Lower Catalyst Loading



performed on 10 mmol scale (1.51 g of oxime **1**) using 3.7 mg of ruthenium complex.

We found that ketoximes such as acetophenone oxime and nitrones were inert to the reaction conditions. The rearrangement of one oxime in the presence of a different nitrile afforded a mixture of amides and nitriles (Scheme 4),

Scheme 4. Crossover Experiment with a Nitrile



suggesting that the reaction pathway involves dehydration of the oxime to a nitrile (or coordinated nitrile), followed by hydration to give the amide. However, in the absence of the oxime, nitriles were inert to hydrolysis with water, although the hydrolysis of nitriles with some ruthenium complexes is known.[15]

Therefore, the active catalyst must remove water from the oxime to give an intermediate which is capable of hydrolyzing the nitrile. One possibility is the formation of a ruthenium hydride species such as $L_nRu(H)(OH)$, which can be formed from the oxime but cannot be formed from water.

In summary, oximes can be converted efficiently into amides with very high selectivity using a ruthenium-based catalyst. Isolation of the amide products is straightforward.[16]

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Supporting Information Available: Details of experimental procedures and characterization data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521.

(16) **Representative Procedure for Formation of Amides from Oximes.** To an oven-dried, nitrogen-purged Schlenk tube containing oxime (5 mmol), $Ru(PPh_3)_3(CO)H_2$ (9.2 mg, 0.01 mmol), dppe (4.0 mg, 0.01 mmol), and *p*-toluenesulfonic acid (7.7 mg, 0.04 mmol) was added degassed anhydrous toluene (5 cm^3) and the mixture heated at reflux for 6 h. On completion, the reaction was allowed to cool to room temperature and diluted with methanol and the solvent removed in vacuo. The crude product was purified by column chromatography on silica gel (methanol/dichloromethane as eluent) or recrystallization from suitable solvent(s), affording the corresponding amide in excellent yield.