Alcohol cross-coupling reactions catalyzed by Ru and Ir terpyridine complexes†

Dinakar Gnanamgari, Chin Hin Leung, Nathan D. Schley, Sheena T. Hilton and Robert H. Crabtree*

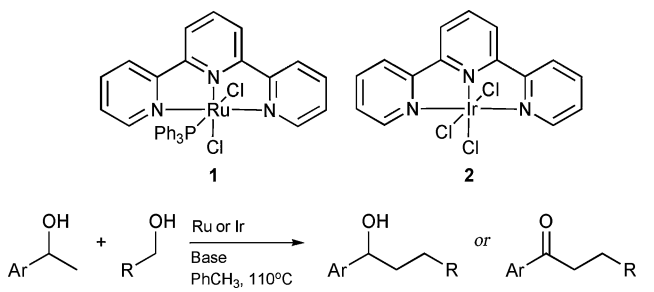
Received 5th September 2008, Accepted 12th September 2008
First published as an Advance Article on the web 17th October 2008
DOI: 10.1039/b815547j

Primary alcohols can be coupled with secondary benzylic alcohols by an air-stable catalytic system involving terpyridine ruthenium or iridium complexes.

Organometallic catalysis has typically employed Cp, PR_3 or NHC ligands.[1] The NNN pincer, 2,2′;6′,2″-terpyridine (terpy), although useful in coordination chemistry[2] and molecular recognition,[3] has rarely been used in organometallic catalysis.[4] Terpy has been considered as an unusually strong π-acceptor relative to other N-donors[5] and is also both oxidatively and thermally robust.[6] Apart from the metal-catalyzed oxidation reaction,[7] there are a few examples of M-terpy complexes as catalysts in asymmetric cyclopropanation,[8] oxidation[9] and dehydrogenation[10] of alcohols, transfer hydrogenation of ketones,[11] nitrene transfer,[12] co-oligomerization of alkenes,[13] allylic alkylation,[14] hydrosilylation,[15] Negishi Coupling,[16] and rearrangement of oxaziridines.[17]

In recent years, an alcohol activation strategy for C–C and C–N coupling reactions has received increasing attention in part because of the potential to replace toxic alkyl halides with relatively benign alcohols in alkylation chemistry.[18,19] For example, β-alkylation of secondary alcohols with primary alcohols to give a coupled alcohol produces water as the sole byproduct and thus with high atom economy.[20]

We now report that [(terpy)Ru(PPh_3)Cl_2] (**1**) and [(terpy)$IrCl_3$] (**2**) catalyze cross-coupling of alcohols[20c] as shown in eqn (1), where Ar can be a variety or aryl groups and R is an aliphatic chain.



(1)

Complexes **1** and **2** were synthesized from terpy and $RuCl_2(PPh_3)_3$ or $IrCl_3$.[21] Among the novel points that come out of the present work, **1** and **2** have higher activity relative to prior systems,[20] achieving full conversion of the substrates in as little as 1 h.[22] For **1**, the catalytic reactions can be run under air but catalyst **2** requires a nitrogen atmosphere. Catalyst **2** can operate effectively under neat conditions.

Table 1 A comparison of catalysts[a]

Entry	Catalyst	Conversion[b]	Yield[c]	Alcohol/ketone
1	**1**	94%	65%	100 : 0
2	**2**[d]	76%	73%	90 : 10
3	terpyRuCl$_3$	83%	58%	100 : 0
4	[Ru(*p*-cymene)Cl$_2$]$_2$	< 5%	—	—
5	RuCl$_2$(PPh$_3$)$_3$	20%	10%	100 : 0
6	[Cp*RuCl$_2$]$_2$	< 5%	—	92 : 8
7	[Cp*IrCl$_2$]$_2$	< 5%	—	—

[a] Conditions: 2.5 mmol 1-phenylethanol and benzyl alcohol, 100 mol% KOH, 1 mol% catalyst in 0.5 mL refluxing toluene under aerobic conditions. [b] Conversions were determined by the consumption of the 2° alcohol. [c] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [d] In sealed vial.

Table 1 compares **1** and **2** with a number of prior alcohol activation catalysts and control complexes. The Cp* and *p*-cymene complexes were essentially inactive under these conditions, but $RuCl_2(PPh_3)_3$ showed weak activity with selectivity analogous to that of **1**. The PPh_3 ligand of **1** has a surprisingly small effect, (terpy)$RuCl_3$ having very comparable activity. We assume reduction to Ru(II) occurs in the reducing medium. This suggests that the N-donor ligand has a much more important role than the PPh_3. $IrCl_3$ hydrate, Pd/C, Ir/C and Rh/C showed no significant activity in our screening.

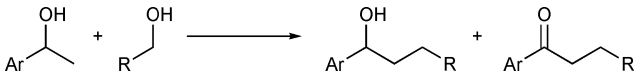
In optimizing conditions for catalyst **1**, a 100% loading of KOH relative to PhCHOHMe with 1% catalyst in toluene proved best (94% conversion, 1 h). The reaction could also be run in the absence of solvent with lower conversion (80% conv.; 55% yield; alcohol/ketone 100 : 0). K_2CO_3 was inactive and KO^{t}Bu gave results only slightly inferior to KOH (90% conv.; 60% yield). Although a strong base, $Ca(OH)_2$ was inactive, probably because of its very low solubility in the medium. Catalyst **2** showed similar behavior to **1** with the various bases, except that a substoichiometric amount (20% relative to alcohol) of KOH proved adequate. Solventless conditions gave better yields than with toluene as solvent. In a sealed vial, ketone production is kept at around 10% of the product. On the other hand, opening the reaction mixture to the atmosphere enhances ketone production up to *ca.* 70% of the products in 3 h, possibly due to oxidation by oxygen.

The scope of the reaction is shown in Table 2. The reaction was tolerant of a number of functional groups. Catalyst **1** showed

Yale Chemistry Department, 225 Prospect St., New Haven, CT 06511, USA. E-mail: robert.crabtree@yale.edu; Fax: +1 203 432 6144; Tel: 1 203 432 3915

† Electronic supplementary information (ESI) available: Optimization of reaction conditions and NMR spectra. See DOI: 10.1039/b815547j

Table 2 β-Alkylation of secondary alcohols with primary alcohols catalyzed by **1** and **2**[a]

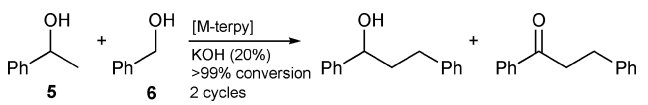


Entry	Ar	R	Catalyst	t (h)	Conversion[b]	Yield[c]	Alcohol : ketone
1	Ph	Ph	**1**	1	94%	65%	100 : 0
2	Ph	4-*n*BuOC$_6$H$_4$	**1**	2	90%	60%[d]	100 : 0
3	Ph	4-ClC$_6$H$_4$	**1**	2	82%	56%	100 : 0
4	Ph	4-MeC$_6$H$_4$	**1**	2	95%	62%	100 : 0
5	Ph	4-*t*BuC$_6$H$_4$	**1**	1	83%	61%[d]	100 : 0
6	Ph	PhCH$_2$	**1**	4	83%	72%	89 : 11
7	Ph	*n*Pr	**1**	4	95%	84%	90 : 10
8	Ph	*i*Pr	**1**	7	82%	70%	90 : 10
9	4-ClC$_6$H$_4$	Ph	**1**	2	87%	61%	100 : 0
10	4-MeC$_6$H$_4$	Ph	**1**	2	95%	66%	100 : 0
11	Ph	Ph	**2**	0.5	99%	95%	93 : 7
12	Ph	*n*Pr	**2**	3	74%	65%	93 : 7
13	Ph	4-ClC$_6$H$_4$	**2**	2	95%	95%	96 : 4
14	Ph	4-*n*BuOC$_6$H$_4$	**2**	2	99%	88%[d]	92 : 8
15	Ph	4-*t*BuC$_6$H$_4$	**2**	2	94%	77%[d]	88 : 12

[a] Conditions: Catalyst **1**: 2.5 mmol of 1° and 2° alcohols, 100 mol% KOH, 1 mol% catalyst in 0.5 mL refluxing toluene under aerobic conditions. Catalyst **2**: 2.5 mmol of 1° and 2° alcohols, 20 mol% KOH, 1 mol% catalyst, neat at 120 °C under N_2. [b] Conversions were determined by the consumption of the 2° alcohol. [c] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [d] Isolated yield.

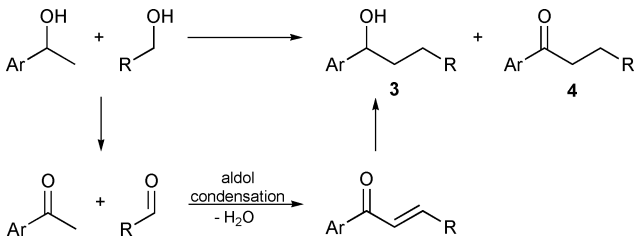
excellent selectivity for producing the coupled alcohol product. Moving to aliphatic primary alcohols still gave the desired products, except that a small amount of ketone was sometimes seen and the reaction required longer times for completion. The yield of products detectable in the solution phase and subsequently isolated did not correspond to the conversion. Some of the material (5–30%) seems to be converted to an insoluble polymer. Catalyst **2** gives a somewhat higher yield for most substrates but is less selective, giving up to 12% ketone.

A small amount of undissolved matter also appeared in the course of the reaction of catalyst **2**, but it does not appear to be involved in catalysis. In an experiment conducted with **2**, filtering a spent reaction mixture (1 h of heating, +99% complete conversion of starting materials) through Celite 545 and then recharging with 1 equivalent of substrates and 20% KOH, led to almost complete conversion to the coupled products after an extra hour of heating. Similarly, recharging a spent reaction of **1** with new substrates and KOH resulted in complete conversion to the corresponding alcohol [eqn (2)].



(2)

β-Alkylation of alcohols is normally ascribed to a hydrogen borrowing process[19b] [eqn (3)] involving a) alcohol dehydrogenation; b) aldol condensation with loss of water from the resulting alcohol; and c) reduction to furnish the saturated product. Essentially all the hydrogen removed in the first step is used to hydrogenate the aldol enone in the final step. A similar mechanism was proposed by Fujita and coworkers.[20c]



(3)

Two probable aldol products should be formed when both components can enolize. In fact, only the products shown (**3** and **4**) are formed, implying that the enolate nucleophile arises exclusively from the secondary alcohol. This could be a result of the presence of the Ar nucleus, because the enol is then a conjugated, unhindered styryl system. Mechanistic studies are under way to determine the selectivity patterns observed.

Conclusions

We report efficient terpy Ru and Ir catalysts for β-alkylation of secondary alcohols with primary alcohols that are superior to prior systems. This green reaction is highly atom economical as it only produces H_2O as a byproduct. The present system does not need any hydrogen donors or acceptors.

Experimental

TerpyRuPPh$_3$Cl[21b] (**1**), terpyRuCl$_3$,[21b] terpyIrCl$_3$,[21a] (**2**), [Ru(*p*-cymene)Cl$_2$]$_2$,[23] RuCl$_2$(PPh$_3$)$_3$,[24] [Cp*RuCl$_2$]$_2$,[25] [Cp*IrCl$_2$]$_2$[26] were all prepared according to known procedures. All the solvents were used as received. All the reagents were received from Aldrich and used as is without any further purification. All the catalytic runs for catalyst **1** were conducted under air without any special precautions. Catalyst **2** required a N_2 atmosphere. NMR spectra

were recorded at room temperature using $CDCl_3$ on 400 and 500 MHz Bruker spectrometers and referenced to the internal standard peak (δ in ppm and J in Hz). Column chromatography was performed using 230–400 mesh silica gel from EMD chemicals Inc. HRMS was performed using 9.4T Bruker Qe FT-ICR MS at the Keck Biotechnology Resource Laboratory (New Haven, CT).

General procedure for catalytic β-alkylation of secondary alcohols with primary alcohols

Catalyst 1. 2.5 mmol of both secondary and primary alcohol, 1,3,5-trimethoxybenzene, KOH (100 mol%), and the catalyst (1 mol%) were combined in a Schlenk tube with toluene (0.5 mL) as solvent and refluxed for the appropriate amount of time. The mixture was then cooled to room temperature and was diluted with CH_2Cl_2 (2.0 mL). The mixture was then filtered through a Celite filter to remove the insoluble inorganic material. An aliquot was then taken from the reaction mixture and diluted with $CDCl_3$. Conversions and yields were determined by comparing to the internal standard.

Catalyst 2. A 5 mL Schlenk tube equipped with a stir bar was charged with 1.0 mmol of each of the substrates, KOH (20 mol%), and catalyst **2** (1 mol%). It then went under three freeze-pump-thaw cycles and was heated under an atmosphere of N_2 in a 120 °C oil bath for the specified amount of time. $CDCl_3$ and *ca.* 10 mg of 1,3,5-trimethoxybenzene as an internal standard was added at the end of the reaction time for determination of yield.

Synthesis of 3-(4-butoxyphenyl)-1-phenylpropan-1-ol from 1

2.5 mmol of 1-phenylethanol and of 4-butoxybenzyl alcohol were combined with KOH (100 mol%), and the catalyst **1** (1 mol%) in a Schlenk tube with toluene (0.5 mL) as solvent and refluxed for 2 h. The mixture was then cooled to room temperature and diluted with CH_2Cl_2 (2.0 mL). The mixture was then filtered through a Celite filter and the resultant mixture was separated using silica gel (2% acetone/toluene). The desired compound was isolated as a colorless liquid (427 mg, 60% yield). The compound was dried under vacuum. ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.54–6.58 (9H, m), 4.63 (1H, ddd, J 3.0, 5.3, 8.0), 3.91 (2H, t, J 6.5), 2.78–2.42 (2H, m), 2.17–1.87 (2H, m), 1.82–1.66 (2H, m), 1.58–1.34 (2H, m), 1.14–0.77 (3H, m). ^{13}C {^{1}H} NMR: δ (126 MHz) 157.34, 144.75, 133.69, 129.29, 128.43, 127.48, 125.98, 114.48, 73.71, 67.72, 40.73, 31.42, 31.14, 19.30, 13.91. HRMS calcd (found) for $C_{19}H_{24}O_2$ M^+:284.1776 (284.1769).

Synthesis of 3-(4-butoxyphenyl)-1-phenylpropan-1-ol and 3-(4-butoxyphenyl)-1-phenylpropan-1-one from 2

2.01 mmol of 4-butoxybenzyl alcohol and of 1-phenylethanol, 0.02 mmol of catalyst **2** (1 mol%) and 0.4 mmol of KOH (20 mol%) were combined as in the general procedure described above. After 1 h the reaction mixture was filtered through Celite and separated by silica gel (2% acetone/toluene). Yields 1.63 mmol of 3-(4-butoxyphenyl)-1-phenylpropan-1-ol (81% yield) and 0.14 mmol of 3-(4-butoxyphenyl)-1-phenylpropan-1-one (7% yield) as colorless oils.

3-(4-Butoxyphenyl)-1-phenylpropan-1-one

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, J 7.6 Hz), 7.47 (1H, t, J 7.6 Hz), 7.36 (2H, t, J 7.6 Hz), 7.07 (2H, d, J 8.8 Hz), 6.75 (2H, 2d, J 8.8 Hz), 3.85 (2H, t, J 6.4), 3.18 (2H, t, J 7.5 Hz), 2.92 (2H, t, J 7.5 Hz), 1.71–1.64 (2H, m), 1.43–1.37 (2H, m), 0.89 (3H, t, 7.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.63, 157.73, 137.05, 133.22, 129.49, 128.77, 128.22, 114.71, 77.55, 77.23, 76.91, 67.87, 40.93, 31.54, 29.47, 19.44, 14.06. HRMS calcd (found) for $C_{19}H_{22}O_2$ M^+: 283.1695 (283.1692)

Synthesis of 3-(4-*tert*-butylphenyl)-1-phenylpropan-1-ol from 1

The same procedure as above and the mixture was separated using silica gel using a gradient column (ethyl acetate/hexanes). The desired compound was isolated as a yellow liquid (409 mg, 61% yield). The compound was dried under vacuum. ^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.37–7.06 (9H, m), 4.67 (1H, dd, J 5.4, 7.7), 2.80–2.53 (2H, m), 2.20–1.87 (2H, m), 1.29 (9H, s). ^{13}C {^{1}H} NMR: δ (126 MHz) 148.77, 144.74, 138.78, 128.61, 128.19, 127.72, 126.07, 125.40, 74.24, 40.79, 34.48, 31.62, 29.84. HRMS calcd (found) for $C_{19}H_{24}O$ M^+: 268.1827 (268.1820).

Synthesis of 3-(4-*tert*-butylphenyl)-1-phenylpropan-1-ol and 3-(4-*tert*-butylphenyl)-1-phenylpropan-1-one from 2

Analogous to method described above for **2**. 2.04 mmol of substrates used, product mixture eluted from column of silica gel (1 : 9 ethyl acetate/hexanes). Yields 1.39 mmol of 3-(4-*tert*-butylphenyl)-1-phenylpropan-1-ol (68% yield) and 0.19 mmol 3-(4-*tert*-butylphenyl)-1-phenylpropan-1-one (9.3%) as colorless oils. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, J 7.6 Hz), 7.54 (1H, t, J 7.6 Hz), 7.45–7.42 (2H, m), 7.31 (2H, d, J 8.7 Hz), 7.18 (2H, d, J 8.7 Hz), 3.29 (2H, t, J 7.6 Hz), 3.02 (2H, t, J 7.6 Hz), 1.29 (3 H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.32, 148.85, 138.07, 136.74, 132.94, 128.48, 127.94, 125.31, 40.38, 34.27, 31.27, 29.44. HRMS calcd (found) for $C_{19}H_{22}O$ M^+: 267.1743 (267.1742).

Notes and references

1 R. H. Crabtree, *J. Organomet. Chem.*, 2005, **690**, 5451–5457.
2 (*a*) E. Baranoff, J. P. Collin, L. Flamigni and J. P. Sauvage, *Chem. Soc. Rev.*, 2004, **33**, 147–155; (*b*) P. Pechy, F. P. Rotzinger, M. K. Nazeeruddin, O. Kohle, S. M. Zakeeruddin, R. Humphrybaker and M. Gratzel, *J. Chem. Soc. Chem. Commun.*, 1995, 65–66.
3 U. S. Schubert, H. Hofmeier and G. R. Newkome, *Modern Terpyridine Chemistry*, Wiley-VCH, Weinheim, 2006.
4 (*a*) X. Sala, N. Santana, I. Serrano, E. Plantalech, I. Romero, M. Rodriguez, A. Llobet, S. Jansat, M. Gomez and X. Fontrodona, *Eur. J. Inorg. Chem.*, 2007, 5207–5214; (*b*) M. K. Tse, H. Jiao, G. Anilkumar, B. Bitterlich, F. G. Gelalcha and M. Beller, *J. Organomet. Chem.*, 2006, **691**, 4419–4433; (*c*) G. Chelucci, A. Saba, D. Vignola and C. Solinas, *Tetrahedron*, 2001, **57**, 1099–1104; (*d*) F. Fagalde, N. D. L. De Katz and N. E. Katz, *J. Coord. Chem.*, 2002, **55**, 587–593.
5 A. Czap, F. W. Heinemann and R. van Eldik, *Inorg. Chem.*, 2004, **43**, 7832–7843.
6 C. M. Che, C. Ho and T. C. Lau, *J. Chem. Soc. Dalton Trans.*, 1991, 1901–1907.
7 J. Limburg, J. S. Vrettos, L. M. Liable-Sands, A. L. Rheingold, R. H. Crabtree and G. W. Brudvig, *Science*, 1999, **283**, 1524–1527.
8 (*a*) C. T. Yeung, P. F. Teng, H. L. Yeung, W. T. Wongb and H. L. Kwong, *Org. Biomol. Chem.*, 2007, **5**, 3859–3864; (*b*) C. T. Yeung, H. L. Yeung, C. S. Tsang, W. Y. Wong and H. L. Kwong, *Chem. Comm.*, 2007, 5203–5205.
9 F. Shi, K. Tse Man and M. Beller, *Chem. Asian. J.*, 2007, **2**, 411–415.
10 H. Junge, B. Loges and M. Beller, *Chem. Comm.*, 2007, 522–524.

11 S. Enthaler, B. Hagemann, G. Erre, K. Junge and M. Beller, *Chem. Asian. J.*, 2006, **1**, 598–604.
12 Z. Li, X. Ding and C. He, *J. Org. Chem.*, 2006, **71**, 5876–5880.
13 Y. Ura, H. Tsujita, T. A. Mitsudo and T. Kondo, *Bull. Korean Chem. Soc.*, 2007, **28**, 2139–2152.
14 G. Chelucci, V. Caria and A. Saba, *J. Mol. Catal. A: Chem.*, 1998, **130**, 51–55.
15 G. Chelucci, S. Gladiali, M. G. Sanna and H. Brunner, *Tetrahedron: Asymmetry*, 2000, **11**, 3419–3426.
16 (*a*) T. J. Anderson, G. D. Jones and D. A. Vicic, *J. Am. Chem. Soc.*, 2004, **126**, 8100–8101; (*b*) G. D. Jones, C. McFarland, T. J. Anderson and D. A. Vicic, *Chem. Comm.*, 2005, 4211–4213.
17 C. H. Leung, A. M. Voutchkova, R. H. Crabtree, D. Balcells and O. Eisenstein, *Green Chemistry*, 2007, **9**, 976–979.
18 E. Skucas, M.-Y. Ngai, V. Komanduri and M. J. Krische, *Acc. Chem. Res.*, 2007, **40**, 1394–1401.
19 (*a*) G. Guillena, D. J. Ramon and M. Yus, *Angew. Chem. Int. Ed.*, 2007, **46**, 2358–2364; (*b*) M. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555–1575; (*c*) K. Fujita and R. Yamaguchi, *Synlett*, 2005, 560–571.
20 (*a*) C. S. Cho, B. T. Kim, H. S. Kim, T. J. Kim and S. C. Shim, *Organometallics*, 2003, **22**, 3608–3610; (*b*) A. Pontes da Costa, M. Viciano, M. Sanau, M., S. Merino, J. Tejeda, E. Peris and B. Royo, *Organometallics*, 2008, **27**, 1305–1309; (*c*) K. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka and R. Yamaguchi, *Org. Lett.*, 2005, **7**, 4017–4019; (*d*) R. Martinez, D. J. Ramon and M. Yus, *Tetrahedron*, 2006, **62**, 8982–8987; (*e*) M. Viciano, M. Sanau and E. Peris, *Organometallics*, 2007, **26**, 6050–6054; (*f*) R. Martinez, D. J. Ramon and M. Yus, *Tetrahedron*, 2006, **62**, 8988–9001.
21 (*a*) J. P. Collin, I. M. Dixon, J. P. Sauvage, J. A. G. Williams, F. Barigelletti and L. Flamigni, *J. Am. Chem. Soc.*, 1999, **121**, 5009–5016; (*b*) B. P. Sullivan, J. M. Calvert and T. J. Meyer, *Inorg. Chem.*, 1980, **19**, 1404–1407.
22 Other reported systems require reaction times of 10+ hours. For example, $[Cp^*IrCl_2]_2$ has a reaction time of 17 h (Ref. 20c) and Peris and Royo's Cp*IrNHC complex (Ref. 20b) takes 6–9 h.
23 E. Hodson and S. J. Simpson, *Polyhedron*, 2004, **23**, 2695–2707.
24 S. K. Sharma, V. K. Srivastava and R. V. Jasra, *J. Mol. Catal. A: Chem.*, 2006, **245**, 200–209.
25 U. Koelle, J. Kossakowski, D. Grumbine and T. D. Tilley, *Inorg. Synth.*, 1992, **29**, 225–228.
26 R. G. Ball, W. A. G. Graham, D. M. Heinekey, J. K. Hoyano, A. D. McMaster, B. M. Mattson and S. T. Michel, *Inorg. Chem.*, 1990, **29**, 2023–2025.