Copper(II)-catalysed addition of O–H bonds to norbornene†

Jason G. Taylor,[a] Neil Whittall[b] and King Kuok (Mimi) Hii*[a]

Received (in Cambridge, UK) 14th July 2005, Accepted 24th August 2005
First published as an Advance Article on the web 19th September 2005
DOI: 10.1039/b509933a

$Cu(OTf)_2$ is an inexpensive, air- and moisture-stable catalyst for the O–H addition of aliphatic and aromatic acids and alcohols to norbornene.

The direct addition of H–X bonds across unsaturated carbon–carbon bonds represents one of the most atom-economical processes for the synthesis of functionalised molecules.[1] In recent years, there have been several reports of novel catalysts that can facilitate the addition of N–H bonds to alkenes and alkynes (hydroamination reactions).[2] In contrast, there are very few reports of similar addition of O–H bonds.

For non-activated alkenes, certain electrophilic additions could be catalysed by Brønsted acids,[3] but the regioselectivity of the process is dependent on the stability of the carbocation intermediate(s). In certain cases, competitive alkene polymerisation and rearrangement processes can be difficult to control. Obviously, transition metal catalysis can circumvent these problems by offering alternative reaction pathways. Surveying the literature, intramolecular hydroalkoxylation (addition of alcohols) has been largely achieved by the use of late transition metal catalysts such as $[PtCl_2(C_2H_4)]_2$–PR_3,[4] $IrCl_3$–AgOTf[5] and, more recently, $Sn(OTf)_4$.[6] Currently, there are only two known examples of intermolecular metal-catalysed O–H addition to alkenes. The first of these was provided by Oe *et al.*[7,8] Using a catalyst generated from a mixture of $Cp^*RuCl_2(PPh_3)_2$–2AgOTf–diphosphine, the addition of 2-phenylethylethanol to styrene, 1-octene and norbornene can be achieved. Interestingly, the catalyst is also effective for the addition of aromatic carboxylic acids to certain olefins (hydroacyloxylation). Very recently, the addition of phenolic and carboxylic acid nucleophiles to various alkenes was also reported by Yang and He by employing a $(Ph_3P)AuCl$–AgOTf system.[9]

Herein, we report the discovery of a robust and versatile copper catalyst for the addition of acids and alcohols to norbornene.

The addition of 4-methoxybenzoic acid to norbornene was initially examined in the presence of 10 mol% triflic acid (dioxane, 80 °C, 18 h). A low yield of the product ester **1a** was obtained (Table 1, entry 1), suggesting that electrophilic activation of the alkene by the strong Brønsted acid is fairly slow under these reaction conditions. Several cationic metal catalysts were subsequently assessed as potential catalysts, chosen for their well-established Lewis acidity and for their stability to air and moisture (Scheme 1, Table 1). Cationic late-transition metal complexes (ruthenium and rhodium) failed to induce formation of any products, even at 5 mol% loading (entries 2 and 3). In turn, other Lewis acids such as silver, nickel and ytterbium triflate salts produced low to moderate conversions (entries 4–7). Ultimately, copper(II) trifluoromethanesulfonate proved to be a highly active catalyst, affording the norbornyl ester in high yield (entry 8).

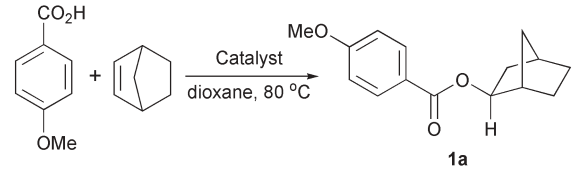
The addition of a selection of *para*-substituted benzoic acid substrates was examined subsequently (Table 2). Employing 2.5 mol% of the copper catalyst, the addition of these acids proceeded smoothly to furnish the corresponding 2-norbornyl esters **1a–d** in good yields (entries 1, 4, 5 and 6). Compared to the cationic ruthenium system,[8] these reactions appear to be relatively insensitive to the electronic property of the nucleophile, although the yield is slightly lower in the presence of electron-withdrawing substituents (entries 5 and 6). As the copper catalyst precursor is employed in the higher oxidation state, we postulated that the exclusion of air and moisture might be unnecessary. Indeed, the reaction can be performed in air with no noticeable decrease in yield (entry 2). The catalyst loading can be further reduced to 1 mol% with a slight decrease in yield (entry 3).

Similarly, the addition of aliphatic and cinnamic acids was also accomplished—giving the corresponding esters **2a–c** in good yields (entries 7–9). These results demonstrate that the current system has a wider synthetic scope than the cationic ruthenium system, which was ineffective for the addition of acetic acid.[7]

Table 1 Addition of 4-methoxybenzoic acid to norbornene in the presence of different catalysts (Scheme 1)[a]

Entry	Catalyst	Catalyst loading (mol%)	Yield (%)[b]
1	TfOH	10	29[c]
2	$[Rh(COD)_2][BF_4]$	5	—
3	$[Cp^*Ru(NCCH_3)_3][PF_6]$	5	—
4	AgOTf	2.5	9
5	$AgBF_4$	2.5	—
6	$Ni(OTf)_2$	2.5	5
7	$Yb(OTf)_3$	2.5	45
8	$Cu(OTf)_2$	2.5	95

[a] General reaction conditions: 4-methoxybenzoic acid (1.0 mmol), norbornene (1.5 mmol), dioxane, 80 °C, 18 h. [b] Isolated yield after column chromatography. The results were duplicated to within ±5%. [c] As a mixture of *exo*- and *endo*- isomers.



1a

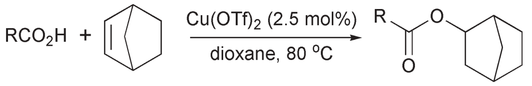
Scheme 1 Catalysed addition of 4-methoxybenzoic acid to norbornene.

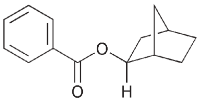
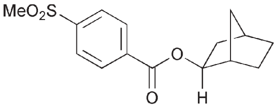
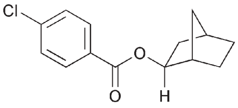
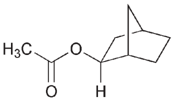
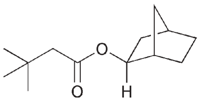
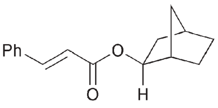
---

[a] *Department of Chemistry, Imperial College London, South Kensington, London, UK SW7 2AZ. E-mail: mimi.hii@imperial.ac.uk; Fax: +44-20-7594-5804; Tel: +44-20-7594-1142*
[b] *GlaxoSmithKline, Old Powder Mills, Nr. Leigh, Tonbridge, Kent, UK TN11 9AN*

† Electronic supplementary information (ESI) available: Full characterisation data of esters and ethers. See http://dx.doi.org/10.1039/b509933a

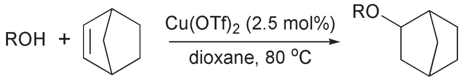
Table 2 Cu(OTf)$_2$-catalysed addition of RCO$_2$H to norbornene[a]

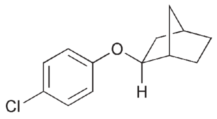
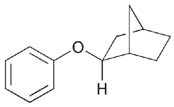
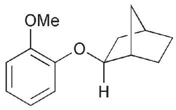
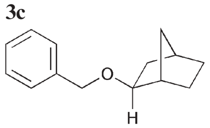
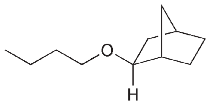
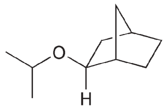
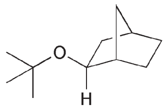


Entry	RCO$_2$H	Product	Yield (%)[b]
1	4-MeOC$_6$H$_5$CO$_2$H	**1a**	95 (90)
2[c]	4-MeOC$_6$H$_4$CO$_2$H	**1a**	97
3[c,d]	4-MeOC$_6$H$_4$CO$_2$H	**1a**	88
4	PhCO$_2$H	 **1b**	95 (70)
5	4-MeSO$_2$C$_6$H$_5$CO$_2$H	 **1c**	80
6	4-ClC$_6$H$_5$CO$_2$H	 **1d**	90
7	CH$_3$CO$_2$H	 **2a**	85 (0)
8	(CH$_3$)$_3$CCH$_2$CO$_2$H	 **2b**	88
9	PhCH=CHCO$_2$H	 **2c**	98

[a] General reaction conditions: Cu(OTf)$_2$ (0.025 mmol), RCO$_2$H (1.0 mmol), norbornene (1.5 mmol), dioxane, 80 °C, 18 h. [b] Isolated yield (based on acid) after column chromatography, duplicated to within ±5%. Value in parenthesis corresponds to that reported using the cationic ruthenium catalyst (ref. 8). [c] Reaction carried out in air. [d] Reaction carried out with 1 mol% catalyst, reaction time 24 h (unoptimised).

Table 3 Cu(OTf)$_2$-catalysed addition of ROH to norbornene[a]



Entry	ROH	Product	Yield (%)[b]
1	4-ClC$_6$H$_5$OH	 **3a**	98
2	PhOH	 **3b**	95
3	2-MeOC$_6$H$_5$OH	 **3c**	97
4	PhCH$_2$OH	 **4a**	98
5	*n*-BuOH	 **4b**	75
6	*i*-PrOH	 **4c**	25
7	*t*-BuOH	 **4d**	0

[a] General reaction conditions: Cu(OTf)$_2$ (0.025 mmol), ROH (1.0 mmol), norbornene (1.0 mmol), dioxane, 80 °C, 18 h. [b] Isolated yield (based on alcohol) after column chromatography, duplicated to within ±3%.

Given the disparity between the properties of acids and alcohols, we were somewhat surprised to discover that the catalyst can also effect the addition of these O–H bonds (Table 3). The electronic and steric properties of the phenolic species appear to exert little influence on the reaction outcome. Even at a reduced substrate ratio of 1 : 1, the addition of the aromatic alcohols proceeded smoothly to furnish aryl ethers **3a–c** with excellent yields (entries 1–3).[10] Correspondingly, the addition of benzyl and *n*-butanol afforded the alkyl ethers **4a** and **4b** in high yields (entries 4 and 5). These reactions are clearly more sensitive to the steric bulk of the alkyl group, as indicated by the dramatic decline in yield as the α-carbon increases its branching (entries 5, 6 and 7).[11]

All the copper-catalysed reactions examined above proceeded with ⩾95% *exo*- selectivity, as determined by ^{1}H NMR spectroscopy of crude product mixtures after column chromatography. These oily residues were subjected to Kugelrühr distillation to provide the *exo*- isomers as analytically pure samples (supporting information†).

Norbornyl esters and ether derivatives are important classes of compounds frequently employed in medicinal chemistry to enhance the biological potency of drugs.[12] For example, Atizoram (CP80633), an aryl norbornyl ether, is a potent PDE4 inhibitor that is highly effective as a topical treatment for atopic dermatitis.[13] Norbornyl esters and ethers are also important ingredients in the flavours and fragrances industry[14]—indeed, most of the products synthesised during the course of this project possess rather pleasant odours.

Pending further mechanistic investigations, it will be premature at present to speculate on the precise nature of the catalytic species involved in these reactions. As these reactions appear to be rather insensitive to the nature of the O–H bond, we favour a mechanism whereby the cationic copper(II) catalyst activates the double bond of the strained alkene by π-coordination, rendering it susceptible to attack by *O*-nucleophiles.

So far, the addition of 4-methoxybenzoic acid to other alkenes, including styrene, hexa-1,3-diene, octa-1,4-diene and limonene, has been unsuccessful under these conditions. Reactions involving other substrates are currently being investigated.

In summary, copper(II) trifluoromethanesulfonate has been found to be a highly active catalyst for the intermolecular hydroalkoxylation and hydroacyloxylation reactions of norbornene under fairly mild, pH neutral conditions. Compared to previously reported systems,[7–9] the catalyst is readily available, cheap, and does not require pre-activation by silver salts. Both aromatic and aliphatic *O*-nucleophiles can be employed—the only exception being very sterically hindered alkyl alcohols. Furthermore, the copper catalyst can be employed under aerobic conditions at low catalyst loading. Given the importance of norbornyl derivatives, these extremely attractive attributes promise to deliver many practical applications.

The authors thank EPSRC and GSK for studentship support.

Notes and references

1 (*a*) M. Beller, J. Seayad, A. Tillack and H. Jiao, *Angew. Chem., Int. Ed.*, 2004, **43**, 3368; (*b*) *Catalytic Heterofunctionalization*, ed. A. Togni and H. Grützmacher, Wiley-VCH, Weinheim, 2001.

2 For recent reviews, see: (*a*) K. C. Hultzsch, *Adv. Synth. Catal.*, 2005, **347**, 367 and references therein; (*b*) I. Bytschkov and S. Doye, *Eur. J. Org. Chem.*, 2003, **6**, 935; (*c*) S. Hong and T. J. Marks, *Acc. Chem. Res.*, 2004, **37**, 673.

3 (*a*) Triflic acid: L. Coulombel and E. Dunach, *Green Chem.*, 2004, **6**, 499; (*b*) Chlorosulfonic acid: *Tetrahedron Lett.*, 2003, **44**, 6651; (*c*) Sulfamic acid:B. Wang, Y. Gu, L. Yang, J. Suo and O. Kenichi, *Catal. Lett.*, 2004, **96**, 71.

4 H. Qian, X. Han and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2004, **126**, 9536.

5 V. H. Grant and B. Liu, *Tetrahedron Lett.*, 2005, **46**, 1237.

6 L. Coulombel, I. Favier and E. Dunach, *Chem. Commun.*, 2005, 2286.

7 Y. Oe, T. Ohta and Y. Ito, *Synlett*, 2005, 179.

8 Y. Oe, T. Ohta and Y. Ito, *Chem. Commun.*, 2004, 1620.

9 C. G. Yang and C. He, *J. Am. Chem. Soc.*, 2005, **127**, 6966. Only one example of the addition (4-methoxybenzoic acid) to norbornene was reported using the gold catalyst—higher catalytic loading (5 mol%) was required for completion of the reaction.

10 An excess (4 equivalents) of the olefin substrate was required using the Au catalyst. A higher catalytic loading of 5 mol% was also required for the addition of carboxylic acids (ref. 9).

11 Unreacted *tert*-butanol was recovered at the end of the reaction, indicating that dehydration of the alcohol is not a competitive process under these conditions. The low isolated yields of the product ethers **4b** and **4c** may also be due to their volatility.

12 For example, see: R. McCague, M. G. Rowlands, S. E. Barrie and J. Houghton, *J. Med. Chem.*, 1990, **33**, 3050.

13 J. M. Hanifin, S. C. Chan, J. B. Cheng, S. J. Tofte, W. R. Henderson, Jr, D. S. Kirby and E. S. Weiner, *J. Invest. Dermatol.*, 1996, **107**, 51.

14 (*a*) M. K. Mamedov, I. N. Gadzhieva and Kh. M. Alimardanov, *Russ. J. Org. Chem.*, 2003, **39**, 180; (*b*) M. K. Amedov, *Russ. J. Org. Chem.*, 1997, **33**, 165; (*c*) J. M. Coxon, R. A. M. Gregson and R. G. Paddick, *Chem. Senses Flavour*, 1978, **3**, 431.