ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 9528–9530

www.rsc.org/chemcomm

COMMUNICATION

Enantioselective alkylation of β-keto phosphonates by direct use of diaryl methanols as electrophiles†

Masashi Shibata, Masahiro Ikeda, Kazuki Motoyama, Yoshihiro Miyake and Yoshiaki Nishibayashi*

Received 21st July 2012, Accepted 5th August 2012
DOI: 10.1039/c2cc35262a

Enantioselective alkylation of β-keto phosphonates with diaryl methanols in the presence of catalytic amounts of copper(II) trifluoromethanesulfonate and an optically active ligand gives the corresponding alkylated products in good to high yields with a high enantioselectivity.

The development of enantioselective carbon–carbon bond forming reactions is of great importance in organic chemistry. Among these reactions, asymmetric direct nucleophilic substitution reactions of alcohols with carbon-centered nucleophiles are expected to provide a useful method for the construction of carbon–carbon bonds to generate optically active centers and have attracted much attention from the environmental and economical points of view because water is the sole by-product of the transformations.[1] Recently, the enantioselective direct substitution reactions of allylic alcohols with a variety of carbon-centered nucleophiles have been extensively studied.[2,3] Since our first successful example of the enantioselective direct substitution reaction of propargylic alcohols with acetone,[4] we have reported asymmetric reactions of propargylic alcohols with a variety of carbon-centered nucleophiles.[5,6] In sharp contrast, the use of simple alcohols such as benzylic alcohols for asymmetric direct substitution reactions has been undeveloped until now. Very recently, several groups have studied these reactions extensively, but applicable carbon-centered nucleophiles are limited to aldehydes, ketones, enamines and dienamines.[7]

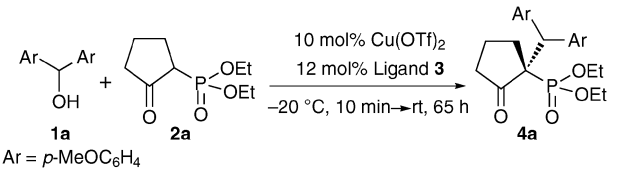
Recently we have continuously studied the application of cooperative catalytic reaction systems using distinct catalysts to enantioselective reactions of propargylic alcohols with carbon-centered nucleophiles such as aldehydes,[8,9] α,β-unsaturated aldehydes,[10] β-keto esters[11] and β-keto phosphonates.[12] Unfortunately, in our reaction system, only propargylic alcohols are available as substrates for direct substitution reactions. In order to develop new cooperative dual catalytic reactions, we have now envisaged that the use of simple alcohols in place of propargylic alcohols may promote the enantioselective alkylation of simple alcohols with various carbon-centered nucleophiles, where copper complex and Brønsted acid cooperatively activate carbon-centered nucleophiles and alcohols, respectively. In fact, the alkylation of β-keto phosphonates proceeded enantioselectively. A preliminary result is described herein.

Treatment of bis(4-methoxyphenyl)methanol (**1a**) with 3 equivalents of diethyl 2-oxocyclopentylphosphonate (**2a**) in the presence of a catalytic amount of copper complex $Cu(OTf)_2$ with (3a*R*,3a′*R*,8a*S*,8a′*S*)-2,2′-(cyclopropylidene)-bis{3a,8a-dihydro-8*H*-indeno[1,2*d*]-oxazole} (**3a**) at −20 °C for 10 min and then at room temperature for 65 h gave diethyl 1-(bis(4-methoxyphenyl)methyl)-2-oxocyclopentylphosphonate (**4a**) in 95% yield with 84% ee (Table 1, Entry 1). This result is in sharp contrast to the result when ethyl 2-oxocyclopentanecarboxylate (**5**) was used as a carbon-centered nucleophile under the same reaction conditions (87% yield, 46% ee). The reaction was carried out in other solvents such as dichloromethane and tetrahydrofuran (THF), and unsatisfactory results were observed in both cases (Table 1, Entries 2–3). Other bis(oxazoline) ligands such as **3b** and **3c** did not work effectively (Table 1, Entries 4–5). On the other hand, no reaction occurred at all when **3d** and **3e** were used as bis(oxazoline) ligands (Table 1, Entries 6–7). Only the use of 1.5 equivalents of **2a** to **1a** was enough to promote the enantioselective alkylation (Table 1, Entry 8). The use of 5 mol% of $Cu(OTf)_2$ substantially decreased the yield of **4a**, although the addition of 5 mol% of trifluoromethanesulfonic acid (HOTf) dramatically improved the yield of **4a** (Table 1, Entries 9–10). These results indicate that HOTf plays an important role in promoting the alkylation effectively.

Next, alkylation of a variety of diaryl methanols **1** was carried out by using $Cu(OTf)_2$ with **3a**. Typical results are shown in Table 2. The introduction of alkoxy substituents at the benzene ring in **1** is necessary to promote the alkylation smoothly. In all cases, the corresponding alkylated products were obtained with a high enantioselectivity (Table 2, Entries 2–8). The highest enantioselectivity (90% ee) was observed when **1g** was used as a substrate (Table 2, Entry 7). The use of 6-methoxy-2-naphthyl and thienyl groups as aromatic moieties in **1** gave slightly lower enantioselectivities (Table 2, Entries 9–10). An asymmetric diaryl methanol such as **1k** reacted

Institute of Engineering Innovation, School of Engineering, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-8656, Japan. E-mail: ynishiba@sogo.t.u-tokyo.ac.jp; Fax: +81-3-5841-1175
† Electronic supplementary information (ESI) available: Experimental section. CCDC 891211. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc35262a

Table 1 Enantioselective alkylation of β-keto phosphonate (**2a**) with alcohol (**1a**)[a]



Entry	Solvent	Ligand	Yield of **4a**[b] (%)	ee[c] (%)
1	$ClCH_2CH_2Cl$	**3a**	95	84
2	CH_2Cl_2	**3a**	68	86
3	THF	**3a**	29	74
4	$ClCH_2CH_2Cl$	**3b**	46	80
5	$ClCH_2CH_2Cl$	**3c**	14	48
6	$ClCH_2CH_2Cl$	**3d**	0	—
7	$ClCH_2CH_2Cl$	**3e**	0	—
8[d]	$ClCH_2CH_2Cl$	**3a**	61	85
9[e]	$ClCH_2CH_2Cl$	**3a**	9	87
10[e,f]	$ClCH_2CH_2Cl$	**3a**	57	86

[a] All reactions of **1a** (0.15 mmol) with **2a** (0.45 mmol) were carried out in the presence of $Cu(OTf)_2$ (0.015 mmol) and **3** (0.018 mmol) in solvent (3.0 mL). [b] Isolated yield. [c] Determined by HPLC. [d] 1.5 equiv. of **2a** were used. [e] 5 mol% of $Cu(OTf)_2$ and 6 mol% of **3a** was used. [f] 5 mol% of HOTf was added.

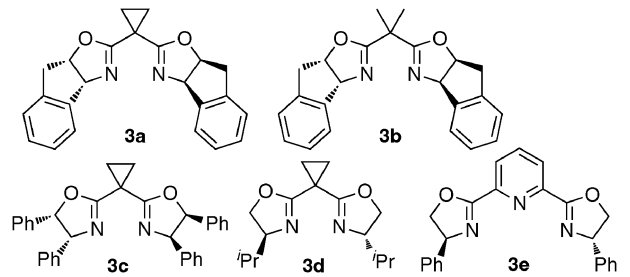
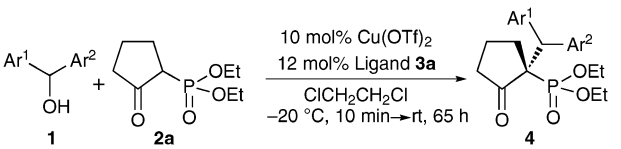


Table 2 Enantioselective alkylation of β-keto phosphonate (**2a**) with alcohols (**1**)[a]



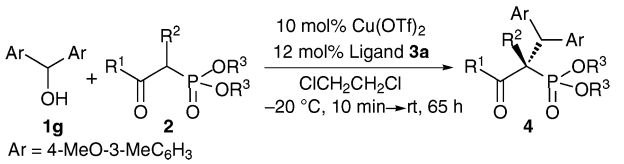
Entry	Alcohol	Yield of **4**[b] (%)	ee[c] (%)
1	$Ar^1 = Ar^2 = p$-$MeOC_6H_4$ (**1a**)	95 (**4a**)	84
2	$Ar^1 = Ar^2 = p$-$EtOC_6H_4$ (**1b**)	82 (**4b**)	88
3	$Ar^1 = Ar^2 = p$-$^n PrOC_6H_4$ (**1c**)	99 (**4c**)	87
4	$Ar^1 = Ar^2 = p$-$^n BuOC_6H_4$ (**1d**)	87 (**4d**)	87
5	$Ar^1 = Ar^2 = p$-$^i PrOC_6H_4$ (**1e**)	95 (**4e**)	87
6[d]	$Ar^1 = Ar^2 = p$-$BnOC_6H_4$ (**1f**)	88 (**4f**)	83
7	$Ar^1 = Ar^2$ = 4-MeO-3-MeC_6H_3 (**1g**)	87 (**4g**)	90
8[e]	$Ar^1 = Ar^2 = 3,4$-$(MeO)_2C_6H_3$ (**1h**)	93 (**4h**)	86
9[f]	$Ar^1 = Ar^2$ = 6-MeO-2-naphthyl (**1i**)	90 (**4i**)	77
10[g]	$Ar^1 = Ar^2$ = 2-thienyl (**1j**)	85 (**4j**)	76
11[h]	Ar^1 = 2-thienyl, Ar^2 = 6-MeO-2-naphthyl (**1k**)	88 (**4k**)[i]	88[j]

[a] All reactions of **1** (0.15 mmol) with **2a** (0.45 mmol) were carried out in the presence of $Cu(OTf)_2$ (0.015 mmol) and **3a** (0.018 mmol) in $ClCH_2CH_2Cl$ (3.0 mL). [b] Isolated yield. [c] Determined by HPLC. [d] rt, 120 h. [e] 40 °C, 40 h. [f] 50 °C, 100 h. [g] 0 °C, 40 h. [h] rt, 45 h. [i] The ratio of diastereoisomers is 1.7/1. [j] The ee of the minor isomer is 64%.

with **2a** under the same reaction conditions to give the corresponding alkylated product (**4k**) as a mixture of two diastereoisomers with a high enantioselectivity (Table 2, Entry 11). Unfortunately, no reaction occurred at all when bis(4-methyphenyl)methanol was used as a substrate. These results indicate that the use of electron-rich aromatic moieties in **1** is necessary to promote the catalytic reaction.

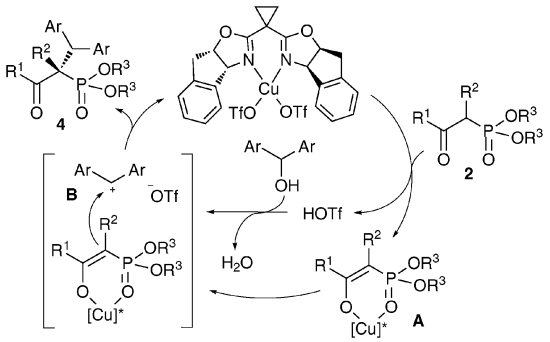
Alkylation with other β-keto phosphonates also proceeded smoothly to give the corresponding alkylated products with a high enantioselectivity. Typical results are shown in Table 3. When methyl, propyl, and butyl groups were used as ester moieties in place of the ethyl groups in **2a**, a similar high enantioselectivity was observed in all cases (Table 3, Entries 2–5). The reaction of **1g** with β-keto phosphonates bearing an indane skeleton (**2f**) under the same reaction conditions gave the corresponding alkylated product in 93% yield with 85% ee (Table 3, Entry 6). The use of diethyl 2-oxotetrahydrofuran-3-ylphosphonate and diethyl 3,3-dimethyl-2-oxocyclopentylphosphonate under the same reaction conditions gave **4q** and **4r** with a slightly lower enantioselectivities (Table 3, Entries 7–8). The reaction with diethyl 2-oxocyclohexylphosphonate did not proceed smoothly although a high enantioselectivity was

Table 3 Enantioselective alkylation of β-keto phosphonates (**2**) with alcohol (**1g**)[a]

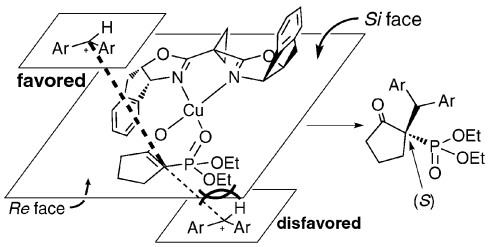


Entry	Phosphonate		Yield of **4**[b] (%)	ee[c] (%)
1		R^3 = Et (**2a**)	87 (**4g**)	90
2[d]		R^3 = Me (**2b**)	73 (**4l**)	86
3		R^3 = ^{n}Pr (**2c**)	95 (**4m**)	90
4		R^3 = ^{n}Bu (**2d**)	89 (**4n**)	88
5		R^3 = ^{i}Pr (**2e**)	93 (**4o**)	92
6[e]		(**2f**)	93 (**4p**)	85
7[f]		(**2g**)	64 (**4q**)	74
8[g]		(**2h**)	78 (**4r**)	66
9[d]		(**2i**)	8 (**4s**)	88
10[d]		(**2j**)	59 (**4t**)	42

[a] All reactions of **1g** (0.15 mmol) with **2** (0.45 mmol) were carried out in the presence of $Cu(OTf)_2$ (0.015 mmol) and **3a** (0.018 mmol) in $ClCH_2CH_2Cl$ (3.0 mL). [b] Isolated yield. [c] Determined by HPLC. [d] rt, 120 h. [e] rt, 40 h. [f] 50 °C, 65 h. [g] 40 °C, 65 h.



Scheme 1 Proposed reaction pathway for the enantioselective alkylation of β-keto phosphonates with alcohols.



Scheme 2 Asymmetric induction of alkylation between a benzyl cation and copper–enolate complex.

observed (Table 3, Entry 9). Only a moderate enantioselectivity was observed when acyclic phosphonates such as diethyl 3-oxobutan-2-ylphosphonate (**2j**) were used (Table 3, Entry 10). These results indicate that the use of β-keto phosphonates bearing a 2-oxocyclopentyl moiety at the α-position in **2** is necessary to obtain the corresponding alkylated products in good to high yields with a high enantioselectivity.

A proposed reaction pathway is shown in Scheme 1. The initial step is the formation of an enolate (**A**) generated *in situ* from β-keto phosphonate **2** and $Cu(OTf)_2$ bearing **3a**. Subsequent attack of **A** upon a benzyl cation (**B**), which is formed from a diaryl methanol and HOTf, results in the formation of the alkylated product (**4**).

After the conversion of **4a** into the corresponding phosphonic acid **6** and one recrystallization of **6**, the enantiomerically pure **6** was isolated, and its absolute configuration was determined as *S* by X-ray analysis.† To account for the enantioselective formation of (*S*)-**6**, we propose transition states between the benzyl cation and the copper–enolate complex in Scheme 2. In this reaction system, the square-planar-like copper–enolate proposed by Jørgensen and co-worker[13] attacks the benzyl cation from the *Si*-face of the enolate leading to the carbon–carbon bond formation.

In summary, we have found the copper- and Brønsted acid-catalyzed enantioselective alkylation of β-keto phosphonates by direct use of diaryl methanols as electrophiles to give the corresponding alkylated products in excellent yields with high enantioselectivities (up to 92% ee). We believe that the findings described herein will open up not only a new type of enantioselective direct substitution reaction of simple alcohols but also a new aspect of cooperative catalytic reactions using distinct catalysts such as transition metal and Brønsted acid catalysts to achieve more valuable transformations that could not be realized by single catalysts. Further work is currently in progress to apply this strategy to other reaction systems.

This work was supported by the Funding Program for Next Generation World-Leading Researchers (GR025) and a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT, Japan.

Notes and references

1 For recent reviews on achiral direct substitution reactions of alcohols with various nucleophiles, see: (*a*) J. Muzart, *Tetrahedron*, 2005, **61**, 4179; (*b*) Y. Tamaru, *Eur. J. Org. Chem.*, 2005, 2647; (*c*) J. Muzart, *Eur. J. Org. Chem.*, 2007, 3077; (*d*) E. Emer, R. Sinisi, M. G. Capdevila, D. Petruzziello, F. De Vincentiis and P. G. Cozzi, *Eur. J. Org. Chem.*, 2011, 647.

2 For recent reviews on enantioselective substitution reactions of allylic alcohols. see: (*a*) B. Sundararaju, M. Achard and C. Bruneau, *Chem. Soc. Rev.*, 2012, **41**, 4467; (*b*) M. Bandini, G. Cera and M. Chiarucci, *Synthesis*, 2012, 504.

3 For selected recent examples, see: (*a*) C. García-Yebra, J. P. Janssen, F. Rominger and G. Helmchen, *Organometallics*, 2004, **23**, 5459; (*b*) B. M. Trost and J. Quancard, *J. Am. Chem. Soc.*, 2006, **128**, 6314; (*c*) M. G. Capdevila, F. Benfatti, L. Zoli, M. Stenta and P. G. Cozzi, *Chem.–Eur. J.*, 2010, **16**, 11237; (*d*) G. Jiang and B. List, *Angew. Chem., Int. Ed.*, 2011, **50**, 9471.

4 Y. Inada, Y. Nishibayashi and S. Uemura, *Angew. Chem., Int. Ed.*, 2005, **44**, 7715.

5 For recent reviews on catalytic propargylic substitution reactions of propargylic alcohols with various nucleophiles, see: (*a*) Y. Miyake, S. Uemura and Y. Nishibayashi, *ChemCatChem*, 2009, **1**, 342; (*b*) R. J. Detz, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2009, 6263; (*c*) C.-H. Ding and X.-L. Hou, *Chem. Rev.*, 2011, **111**, 1914; (*d*) Y. Nishibayashi, *Synthesis*, 2012, 489.

6 (*a*) H. Matsuzawa, Y. Miyake and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2007, **46**, 6488; (*b*) H. Matsuzawa, K. Kanao, Y. Miyake and Y. Nishibayashi, *Org. Lett.*, 2007, **9**, 5561; (*c*) K. Fukamizu, Y. Miyake and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2008, **130**, 10498; (*d*) K. Kanao, Y. Miyake and Y. Nishibayashi, *Organometallics*, 2009, **28**, 2920; (*e*) K. Kanao, Y. Miyake and Y. Nishibayashi, *Organometallics*, 2010, **29**, 2126.

7 For selected recent examples, see: (*a*) P. G. Cozzi, F. Benfatti and L. Zoli, *Angew. Chem., Int. Ed.*, 2009, **48**, 1313; (*b*) Q.-X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng and L.-Z. Gong, *Org. Lett.*, 2009, **11**, 4620; (*c*) G. Bergonzini, S. Vera and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2010, **49**, 9685; (*d*) L. Zhang, L. Cui, X. Li, J. Li, S. Luo and J.-P. Cheng, *Chem.–Eur. J.*, 2010, **16**, 2045; (*e*) J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann and M. Christmann, *Org. Lett.*, 2011, **13**, 70; (*f*) J. Xiao, K. Zhao and T.-P. Loh, *Chem.–Asian. J.*, 2011, **6**, 2890; (*g*) B. Xu, Z.-L. Guo, W.-Y. Jin, Z.-P. Wang, Y.-G. Peng and Q.-X. Guo, *Angew. Chem., Int. Ed.*, 2012, **51**, 1059; (*h*) L. Song, Q.-X. Guo, X.-C. Li, J. Tian and Y.-G. Peng, *Angew. Chem., Int. Ed.*, 2012, **51**, 1899; (*i*) J. Xiao, K. Zhao and T.-P. Loh, *Chem. Commun.*, 2012, **48**, 3548; (*j*) M. Trifonidou and C. G. Kokotos, *Eur. J. Org. Chem.*, 2012, 1563.

8 (*a*) M. Ikeda, Y. Miyake and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2010, **49**, 7289; (*b*) K. Motoyama, M. Ikeda, Y. Miyake and Y. Nishibayashi, *Eur. J. Org. Chem.*, 2011, 2239.

9 R. Sinisi, M. V. Vita, A. Gualandi, E. Emer and P. G. Cozzi, *Chem.–Eur. J.*, 2011, **17**, 7404.

10 M. Ikeda, Y. Miyake and Y. Nishibayashi, *Organometallics*, 2012, **31**, 3810.

11 M. Ikeda, Y. Miyake and Y. Nishibayashi, *Chem.–Eur. J.*, 2012, **18**, 3321.

12 K. Motoyama, M. Ikeda, Y. Miyake and Y. Nishibayashi, *Organometallics*, 2012, **31**, 3426.

13 A. Kjærsgaard and K. A. Jørgensen, *Org. Biomol. Chem.*, 2005, **3**, 804.