JOC Note

pubs.acs.org/joc

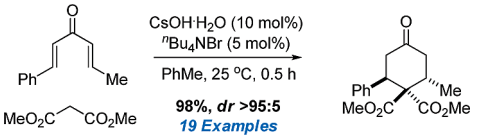
Stereoselective Synthesis of Cyclohexanones via Phase Transfer Catalyzed Double Addition of Nucleophiles to Divinyl Ketones.

Andrew C. Silvanus,[†] Benjamin J. Groombridge,[†] Benjamin I. Andrews,[‡] Gabriele Kociok-Köhn,[†] and David R. Carbery[†,*]

[†]*Department of Chemistry, University of Bath, Bath BA2 7AY, U.K, and* [‡]*GlaxoSmithKline Medicines Research Centre, Stevenage, Hertfordshire SG1 2NY, U.K.*

d.carbery@bath.ac.uk

Received August 31, 2010



Functionalized cyclohexanones are formed in excellent yield and diastereoselectivity from a phase transfer catalyzed double addition of active methylene pronucleophiles to nonsymmetrical divinyl ketones.

The development of single-pot reactions which allow the rapid construction of several bonds and stereocenters remains a considerable challenge in modern organic chemistry.[1] In many instances this strategy can offer a simple and versatile synthesis of valuable building blocks from inexpensive starting materials.

Highly substituted cyclohexanones and the related cyclohexanols, provide key skeletal components of many natural products with significant biological and pharmaceutical importance.[2] In particular, a number of important cyclohexanol natural products exist which have a quaternary center at C-4 (Figure 1). Jiadifenolide **1**[3] and jiadifenin **2**[4] are highly active neurotrophins which possess such a cyclohexanol motif embedded within their compact and complex molecular structure (Figure 1). Therefore, these natural products offer themselves as challenging synthetic targets and have attracted considerable attention.[5]

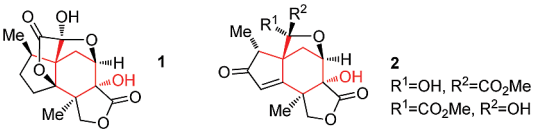
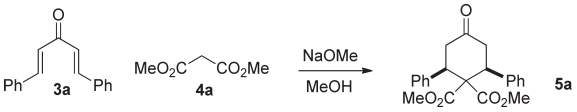


FIGURE 1. Jiadifenolide **1** and jiadifenin **2**.

A number of synthetic routes to functionalized cyclohexanones have been be reported in recent years, underlining the continued importance of this framework to the synthetic community. Most notably [4 + 2] cycloadditions,[2a,6] organocatalyzed domino annulations,[7] Rh(I)-catalyzed Pauson–Khand,[8] Pd-catalyzed intramolecular hydroalkylation,[9] and reductive tandem double Michael cascades.[10]

Divinyl ketones (DVKs) are predominantly associated with the Nazarov reaction.[11] However, they also act as competent double electrophiles reacting with a variety of double nucleophiles.[12] The double addition of a methylene pronucleophile is well-known (Scheme 1).[13]

SCHEME 1. Reaction of a Malonate with a Divinyl Ketone[13]



For example, Kohler reported in 1924 that dibenzylidene acetone **3a** formed *meso*-cyclohexanone **5a** when exposed to dimethylmalonate and NaOH. The reaction is *syn*-selective, with all subsequent reports involving the use of symmetrical diaryl DVKs, or similar pseudosymmetrical diaryl substituted ketones, forming *syn*-diaryl cyclohexanones.[14] The

(1) (a) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (b) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (d) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315. (e) Ho, T. L. *Tandem Organic Reactions*; John Wiley: New York, 1992. (f) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.

(2) (a) Jiang, J.; Bunda, J. L.; Doss, G. A.; Chicchi, G. G.; Kurtz, M. M.; Tsao, K.-L. C.; Tong, X.; Zheng, S.; Upthagrove, A.; K.; Samuel, K.; Tschirret-Guth, R.; Kumar, S.; Wheeldon, A.; Carlson, E. J.; Hargreaves, R.; Burns, D.; Hamill, T.; Ryan, C.; Krause, S. M.; Eng, W.; DeVita, R. J.; Mills, S. G. *J. Med. Chem.* **2009**, *52*, 3039. (b) Bui, T.; Barbas, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951.

(3) Kubo, M.; Okada, C.; Huang, J.-M.; Harada, K.; Hioki, H.; Fukuyama, Y. *Org. Lett.* **2009**, *11*, 5190.

(4) Yokoyama, R.; Huang, J.-M.; Yang, C.-S.; Fukuyama, Y. *J. Nat. Prod.* **2002**, *65*, 527.

(5) For total synthesis of **2**, see: (a) Cho, Y. S.; Carcache, D. A.; Tian, Y.; Li, Y-M; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 14358. (b) Carcache, D. A.; Cho, Y. S.; Hua, Z.; Tian, Y.; Li, Y-M; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1016.

(6) (a) Kim, W. H.; Lee, J. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 12576. (b) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

(7) (a) Pulkkinen, J.; Aburel, P. S.; Halland, N.; Jørgensen, K. A. *Adv. Synth. Catal.* **2004**, *346*, 1077. (b) Gryko, D. *Tetrahedron: Asymmetry* **2005**, *16*, 1377. (c) Wang, J.; Ma, A.; Ma, D. *Org. Lett.* **2008**, *10*, 5425. (d) Hayashi, Y.; Toyoshima, M.; Gotoh, H.; Ishikawa, H. *Org. Lett.* **2009**, *11*, 45. (e) Enders, D.; Erdmann, N.; Raabe, G. *Synthesis* **2010**, 2271.

(8) Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 2528.

(9) Wang, X.; Pei, T.; Han, X.; Widenhoefer, R. A. *Org. Lett.* **2003**, *5*, 2699.

(10) Kamenecka, T. M.; Overman, L. E.; Ly Sakata, S. K. *Org. Lett.* **2002**, *4*, 79.

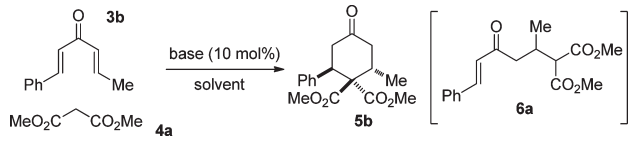
(11) (a) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (b) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193.

(12) For selected heteroatom double additions to divinyl ketones, see: (a) Rosiak, A.; Hoenke, C.; Christoffers, J. *Eur. J. Org. Chem.* **2007**, 4376. (b) Radha Krishna, P.; Sreeshailam, A. *Tetrahedron Lett.* **2007**, *48*, 6924. (c) Rosiak, A.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2006**, 4044. (d) Rosiak, A.; Christoffers, J. *Synlett* **2006**, 1434. (e) Reddy, D. B.; Reddy, A. S.; Padmavathi, V. *Synth. Commun.* **2001**, *31*, 3429. (f) Brenstrum, T.; Clattenburg, J.; Britten, J.; Zavorine, S.; Dyck, J.; Robertson, A. J.; McNulty, J.; Capretta, A. *Org. Lett.* **2006**, *8*, 103.

(13) Kohler, E. P.; Helmkamp, R. W. *J. Am. Chem. Soc.* **1924**, *46*, 1267.

DOI: 10.1021/jo101713d Published on Web 10/13/2010

TABLE 1. Optimisation Study[a]



entry	base	solvent	time (h)	yield **5b** (%)	dr **5b**[b]
1	^{i}PrNEt$_2$	PhMe	24	0[c]	–
2	DBU	PhMe	24	0[c,d]	–
3	NaOMe	PhMe	24	11[c]	91:9
4	NaOH	PhMe	24	5[c]	nd
5	KOH	PhMe	24	3[c]	nd
6	CsOH·H$_2$O	PhMe	24	19[c]	>95:5
7	CsOH·H$_2$O[e]	PhMe	0.5	98	>95:5
8	CsOH·H$_2$O[e]	CH_2Cl_2	0.5	75	71:29
9	CsOH·H$_2$O[e]	CH_3CN	0.5	95	75:25
10	CsOH·H$_2$O[e]	Et_2O	0.5	92	86:14
11	CsOH·H$_2$O[e]	hexane	0.5	84	>95:5

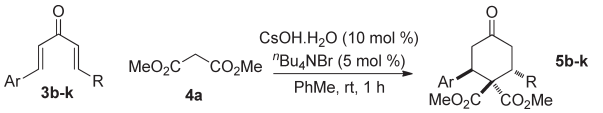
[a]General reaction conditions: base (10 mol %), [1 M] at 25 °C. [b]Measured by ^{1}H NMR analysis of crude reaction mixture. [c]Reaction conversion: measured by ^{1}H NMR analysis of crude reaction mixture. [d]Enone **6a** recovered in 99%. [e]*n*-Bu$_4$NBr (5 mol %) additive used.

limited substrate scope and inherent symmetry of the products suggests a reaction of limited applicability in a stereoselective target-orientated context.

We felt the potential of this annulation had not been fully realized regarding divinyl ketone scope and stereochemical control.[15] Indeed, similar concerns had prompted our recent studies concerning a highly diastereoselective annulation of nonsymmetrical DVKs and indoles.[16] Herein we report studies concerning the double addition of a range of methylene pronucleophiles to nonsymmetrical DVKs. DVK **3b** was chosen as the initial substrate for examination as each enone terminus is sterically and electronically differentiated. Accordingly, dimethyl malonate was exposed to a range of bases at catalytic loadings, with toluene initially examined (Table 1).[17]

Organonitrogen bases were found to be largely ineffective at catalyzing the desired reaction (entries 1−2). However, DBU catalyzed the formation of the monoaddition product **6a** (entry 2). This observation confirmed the order of the stepwise double addition as initial *inter*molecular addition to the Me-substituted enone followed by subsequent cyclization onto the Ph-substituted enone. Catalytic loadings of sodium methoxide and hydroxide bases were also found to be unsuccessful (entries 3−6). However, the formation of the desired cyclohexanone was observed when CsOH was utilized with tetrabutylammonium bromide phase transfer catalyst in toluene solvent (entry 6). This led to a dramatic improvement in reaction efficiency with complete conversion observed in under 30 min when compared with the absence of ^{n}Bu$_4$NBr (entry 5). Application of these phase transfer conditions in other common organic solvents provided no significant improvement to either yield or reaction rate (entries 7−10). Unexpectedly, the *anti*-diastereomer was observed to form in this reaction as ascertained by 1D and 2D ^{1}H NMR spectroscopy. Furthermore, these studies suggested the phenyl group had adopted an axial disposition, in contrast to the *syn*-selectivity reported in all diaryl systems reported in the literature.[14]

TABLE 2. Divinyl Ketone Substrate Scope



entry	R	Ar	product	yield (%)	dr **5** (*anti*/*syn*)[a]
1	Me	Ph	**5b**	98	>95:5
2	Me	4-OMeC$_6$H$_4$	**5c**	64	>95:5
3	Me	2-ClC$_6$H$_4$	**5d**	90	>95:5
4	Me	4-ClC$_6$H$_4$	**5e**	89	>95:5
5	Me	4-MeC$_6$H$_4$	**5f**	93	>95:5
6	Me	3-MeC$_6$H$_4$	**5g**	82	>95:5
7	Me	2-furyl	**5h**	58	>95:5
8	Me	2-pyridyl	**5i**	88	>95:5
9	^{n}Pr	Ph	**5j**	85	>95:5
10	Cy	Ph	**5k**	82[b]	93:7
11	Me	Ph	**5b**	86[c]	>95:5

[a]Measured by ^{1}H NMR analysis of crude reaction mixture. [b]Attempted at 85 °C for 24 h. [c]Conducted on 5 mmol scale for 5 h.

With optimized reaction conditions developed, the scope of the DVK was subsequently examined (Table 2).

The reaction of dimethyl malonate provided access to *anti*-substituted cyclohexanones. In all instances, methyl-aryl substituted DVKs reacted efficiently and with high diastereoselectivity. This reaction allowed for the incorporation of heteroaryl substitution upon the cyclohexanone ring (entries 7−8). In contrast, replacing the methyl group by a cyclohexyl unit led to a dramatic reduction in reactivity with a slight reduction in diastereoselectivity (entry 10). Importantly, this reaction is amenable to being conducted on a larger scale with a 5 mmol scale reaction forming **5b** in 86% (entry 11).

The *anti*-diastereoselectivity of this tandem-sequence was confirmed by X-ray crystallography of cyclohexanone **5c** which also confirmed the axial positioning of the aryl group and equatorial disposition of the methyl group (see Supporting Information).

Having assessed the scope of divinyl ketone electrophile, this methodology was in turn examined with respect to pronucleophile (Table 3).

A range of pronucleophiles reacted smoothly with **3b** to form cyclohexanone products in good yield. The use of symmetrical pronucleophiles resulted in excellent yields and diastereoselctivities (entries 1−3). In contrast, the use of nonsymmetrical active methylene nucleophiles formed diastereomeric mixtures (entries 4−7). Symmetrical methylene pronucleophiles gave excellent levels of *trans*-diastereoselectivity. In general, more acidic pronucleophiles

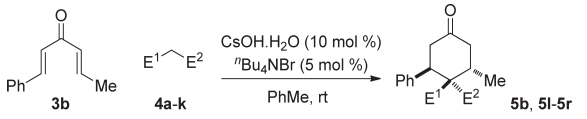
(14) There has been a single example of an *anti*-selective double addition of dimethyl malonates to dibenzylidene acetone, see: Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553.

(15) (a) Li, J-T; Xu, W-Z; Chen, G-F; Li, T.-S. *Ultrason. Sonochem.* **2005**, *12*, 473. (b) Khurana, J. M.; Arora, R.; Satija, S. *Heterocycles* **2007**, *71*, 2709. (c) Padmavathi, V.; Balaiah, A.; Reddy, D. B. *J. Heterocycl. Chem.* **2002**, *39*, 649. (d) Padmavathi, V.; Reddy, B. J. M.; Subbaiah, D. R. C. V.; Padmaja, A. *Indian J. Chem. B* **2006**, *45B*, 808. (e) Padmavathi, V.; Basha, S. M.; Chinna, D. R.; Subbaiah, V.; Reddy, T. V. R.; Padmaja, A. *J. Heterocycl. Chem.* **2005**, *42*, 797. (f) Zhang, D.; Xu, X.; Tan, J.; Liu, Q. *Synlett* **2010**, 917.

(16) Silvanus, A. C.; Heffernan, S. J.; Liptrot, D. J.; Kociok-Köhn, G.; Andrews, B. I.; Carbery, D. R. *Org. Lett.* **2009**, *11*, 1175.

(17) Toluene was initially chosen as solvent due to strong literature precedent of stereoselective phase transfer-catalysed Michael reactions. For reviews of enantioselective phase transfer catalysis, see: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518.

TABLE 3. Pronucleophile Scope



entry	E^1	E^2	time (h)	yield (%)	dr[a]
1	CO_2Me	CO_2Me	0.5	98 (**5b**)	>95:5
2	CN	CN	0.5	97 (**5l**)	>95:5
3[b]			24	48 (**5m**)	>95:5
4	CN	CO_2Me	0.5	92 (**5n**)	81:19:0:0[c,d]
5	C(O)Me	CO_2Me	48	79 (**5o**)	61:39:0:0[c,d]
6	CO_2Me	SO_2Ph	16	82 (**5p**)	75:25:0:0[c,d]
7			16	72 (**5q**)	60:40:0:0[e]
8	H	NO_2	24	0	-

[a]Measured by ^{1}H NMR analysis of crude reaction mixture. [b]Reaction conducted in CH_2Cl_2. [c]Major diastereomer isolable and relative configuration confirmed by NOESY ^{1}H NMR spectroscopy. [d]Minor diastereomer confirmed as epimeric at C-4 quaternary center as confirmed by 1D- and 2D-^{1}H NMR analysis. [e]Major diastereomer not defined, dr value stated.

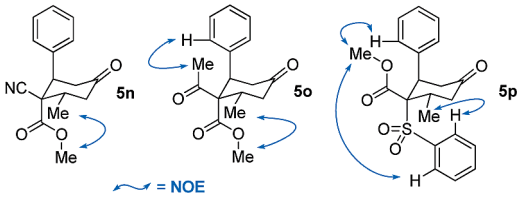
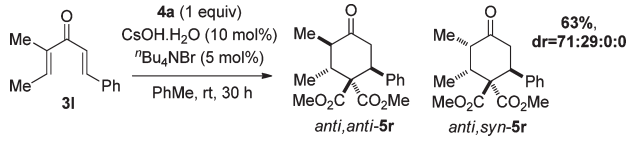


FIGURE 2. Major diastereomer of **5n**−**p** with key NOE interactions.

demonstrated lowered reactivity, presumably a reflection of reduced nucleophilicity of the respective conjugate base as exemplified by the double addition of a β-keto ester pronucleophile (entry 5). Full conversion in this instance took 48 h compared to the short reaction times with malonate and malonitrile pronucleophiles (entries 1−2). The major isomers of **5n**−**p** were isolated after chromatography with the relative configuration confirmed by ^{1}H NOESY spectroscopy (Figure 2).

Efforts have been made to form three stereocenters by employing trisubstututed divinyl ketones (Scheme 2).

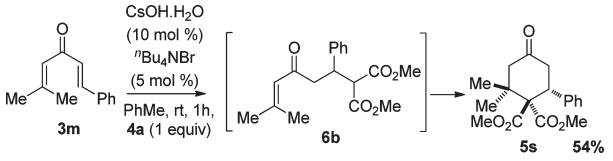
SCHEME 2. Formation of Three Stereocentres



Divinyl ketone **3l** was observed to offer significantly reduced reactivity when compared to the corresponding disubstituted system **3b**. Ultimately, only two diastereomers from a possible four were observed after 30 h and were isolated in 63%, with the major *anti,anti*-diastereomer deduced after extensive 1D- and 2D-NMR spectroscopy. Therefore, complex cyclohexanones with multiple stereocenters are rapidly accessible from divinylketone substrates.

This tandem phase-transfer catalyzed reaction has also allowed access to contiguous quaternary centers. Reaction of dimethyl terminated divinyl ketone **3m** and dimethyl malonate under the developed conditions forms cyclohexanone **5s** in good yield (Scheme 3).

SCHEME 3. Contiguous Quaternary Center Formation[a]



[a]Intermediate enone **6b** isolated in 25%.

In this instance, the initial *inter*molecular Michael reaction is found to occur at the Ph-substituted enone moiety before continuing through a slower *intra*molecular Michael reaction as gauged by the isolation of enone **6b**.

In conclusion, an operationally simple, high-yielding and stereoselective double Michael addition to nonsymmetrical divinyl ketones has been developed. Substrate scope and reactivity trends have been investigated.

Experimental Section

Representative Procedure of Phase Transfer-Catalyzed Double Michael Reactions; Synthesis of 5b. To a vigorously stirring solution of dimethyl malonate (665 μL, 5.3 mmol) and divinyl ketone **3b** (910 mg, 5.3 mmol) in toluene (0.5 M, 10 mL) was added ^{n}Bu$_4$NBr (85 mg, 0.27 mmol, 5 mol %) and CsOH·H$_2$O (79 mg, 0.53 mmol, 10 mol %) at room temperature. The reaction mixture was allowed to stir until TLC analysis showed complete consumption of the starting reagents (5 h). The reaction was quenched by diluting with CH_2Cl_2 (15 mL) and passing through a short pad of silica. The solvent was removed *in vacuo* and crude material purified by flash chromatography (SiO_2, 8:1 petrol/EtOAc) to afford **5b** as a clear oil (1.381 g, 4.56 mmol, 86%, dr > 95:5). FTIR (film/cm^{-1}) υ_{max}: 3628 (w), 2953 (s), 2849 (m), 1754 (s), 1727 (s), 1611 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.23−7.28 (3H, m), 7.04−7.06 (2H, m), 4.03 (1H, dd, J = 7.0, 4.6 Hz), 3.80 (3H, s), 3.46 (3H, s), 3.31 (1H, ddd, J = 15.8, 7.0, 0.8 Hz), 2.96 (1H, dqd, J = 12.0, 6.7, 4.5 Hz), 2.73 (1H, ddd, J = 15.6, 4.5, 1.7 Hz), 2.68 (1H, ddd, J = 15.8, 4.6, 1.7 Hz), 2.29 (1H, ddd, J = 15.6, 12.0, 0.8 Hz), 1.10 (3H, d, J = 6.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 209.8, 170.8, 169.7, 140.4, 128.7, 128.3, 127.6, 61.7, 52.3, 51.9, 46.3, 45.5., 43.9, 32.6, 18.8. HRMS (ES) calcd for $C_{17}H_{20}O_5$ (m/z M + H$^+$): 305.1389. Found 305.1373.

Acknowledgment. The authors are grateful to the EPSRC and GSK for studentship funding (ACS).

Supporting Information Available: Experimental procedures, compound characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.