## A Ru-Catalyzed Four-Component Coupling

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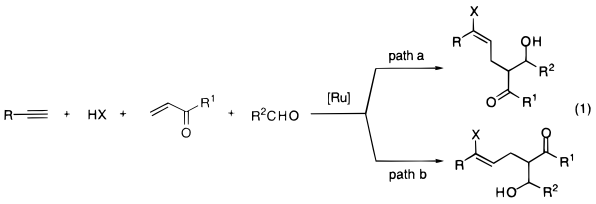
*Received May 15, 2000*

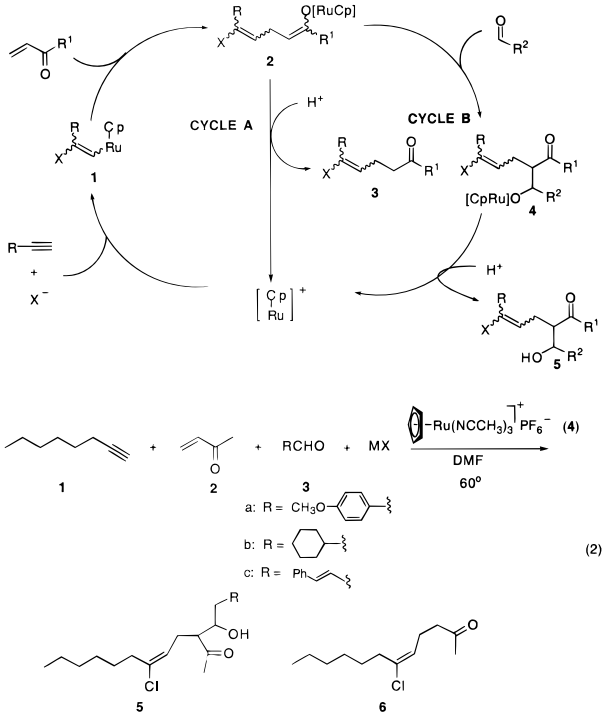
The ability to create molecular complexity rapidly provides for more efficient syntheses of complex molecules. The more bonds that can be formed in a single step, the fewer the number of steps that will be required in a synthetic scheme. Reactions involving the additions of more than two molecules in a single step are uncommon; those that involve four components are rare. The most well-known is the Ugi reaction[1] which has found particular utility in combinatorial strategies.[2] As part of a program to develop atom economical reactions,[3] we have developed a four-component coupling according to eq 1.




Scheme 1 outlines the mechanistic proposal. In our studies of the addition of HX, alkynes, and vinyl ketones catalyzed by a ruthenium complex, we proposed that the initial adduct **1** undergoes coordination of a vinyl ketone and migratory insertion to form a ruthenium enolate **2**, which upon protonation forms the adduct **3** and regenerate the initial ruthenium complex to initiate another cycle (cycle A).[4] Could the initial ruthenium enolate[5] **3** undergo capture by an electrophile other than a proton? An aldehyde seemed to be a reasonable alternative since, increasingly, the ability of organometallic intermediates to undergo carbonyl additions in the presence of protonic media is being developed.[6]

The initial experiment (eq 2) examined the reaction depicted in eq 1 utilizing the optimized conditions for *E*-selective chloroalkylation[4a] (3 equiv of $(CH_3)_4NCl$, 15 mol % of $SnCl_4 \cdot 5H_2O$, 10 mol % of **4**) in the presence of 3 equiv of *p*-methoxybenzaldehyde (**3a**) Gratifyingly, the four-component coupling product **5a**[7] was obtained in 54% yield as an 8.6:1 *E*:*Z* mixture of alkene isomers but each as only a single diastereomer as determined by NMR spectroscopy (>10:1dr). In addition, a 19% yield of the three-component coupling product **6** was also obtained. Switching to tetraethylammonium chloride led to a poorer ratio of **5**:**6** (2:1). Using anhydrous stannic chloride inverted the alkene geometry (1:3.6 *E*:*Z*) of **5** and reduced the yield to 39%; significantly, the product of simple protonation **6** still formed in 15% yield. Use of molecular sieves severely depressed the yield of **5a** (to 15%) but still generated 10% of the product obtained by protonation of **6**. Alternative anhydrous cocatalysts did not improve the reaction. Increasing the amount of aldehyde **3** to 6 equiv improved the yield of **5a** to 62%; whereas, the yield of **6** dropped to 13%.

**Scheme 1.** Mechanistic Proposal for Four-Component Coupling




Using the original conditions, the aldehyde **3** was varied. An aliphatic aldehyde, cyclohexanecarboxaldehyde **3b**, gave the four-component product **5b** in 51% (*E*:*Z* 8:1) also as a single diastereomer each in addition to **6** (23%). Cinnamaldehyde also gave only the "expected" product **5c** (48% yield, *E*:*Z* 6.8:1, dr > 10:1) wherein only MVK served as the Michael acceptor and the unsaturated aldehyde as the carbonyl partner. The chemoselectivity of this example stems from the steric sensitivity of this catalyst whereby monosubstituted double bond substrates react much faster than those bearing disubstitution.[8]

Phenyl vinyl ketone (**7**) reacts equally well (eq 3). With the cyanoalkyne **8a** and *p*-anisaldehyde **3a**, a 58% yield of the four-component coupling product **9a** (*E*:*Z* 8:1) as a single diastereomer in each case in addition to the product of simple protonation **10** (21%) was obtained. Use of the aliphatic aldehydes **3b** or **3d** with cyanoalkyne **8a** and methoxycarbonylalkyne **8b** respectively gave the desired adducts **9b** (*E*:*Z* 7.1:1) and **9c** (*E*:*Z* 12.5:1) as single diastereomers in 44% and 42% yields respectively with **10a** and **10b** being isolated in 23% and 28% yields, respectively.

The complementary *cis*-bromoalkylation[4b] was also examined in the four-component coupling as shown in eq 4 and Table 1.

(1) For a lead reference on the Ugi reaction, see: Ugi, I. *J. Prakt. Chem.* **1997**, *339*, 499. Also: Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1999; Vol. 2, Chapter 4.6.

(2) For some examples of the Ugi reaction and other multicomponent reactions in combinatorial chemistry, see: Domling, A. *Combinatorial Chem., High Throughput Screening* **1998**, *1*, 1. Kobayashi, S. *Chem. Soc. Rev.* **1999**, *28*, 1.

(3) Trost, B. M. *Science* **1991**, *254*, 1471.

(4) (a) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 1988. (b) Trost, B. M.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2000**, *39*, 360.

(5) (a) For some examples of Ru enolates, see: Hartwig, J. F.; Bergman, R. G.; Anderson, R. A. *Organometallics* **1991**, *10*, 3326. Rasley, B. T.; Rapta, M.; Kulawiec, R. J. *Organometallics* **1996**, *15*, 2852. (b) For some examples of metal-catalyzed addition to Michael acceptors followed by aldol reactions, see: Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202. Kiyooka, S.; Shimizu, A.; Torri, S. *Tetrahedron Lett.* **1998**, *39*, 5237. Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331. Revis, A.; Hilty, T. *Tetrahedron Lett.* **1987**, *28*, 4809. (c) For an example of a Ru-catalyzed addition to a Michael acceptor, see: Yi, C. S.; Liu, N. *J. Organomet. Chem.* **1998**, *553*, 157.

(6) For a recent example, see: Loh, T. P.; Zhou, J. R. *Tetrahedron Lett.* **1999**, *40*, 9115.

(7) All new compounds have been characterized spectroscopically, and elemental composition has been established by combustion analysis or high-resolution mass spectroscopy.

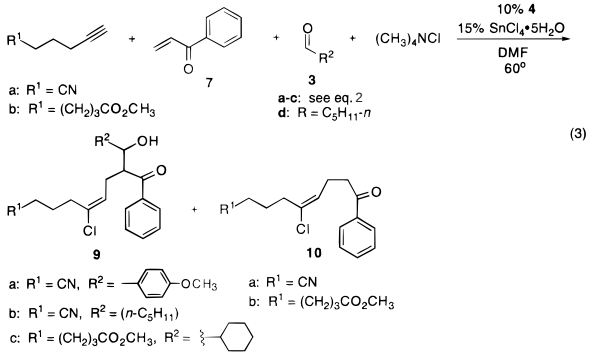
(8) Trost, B. M.; Indolese, A.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615.

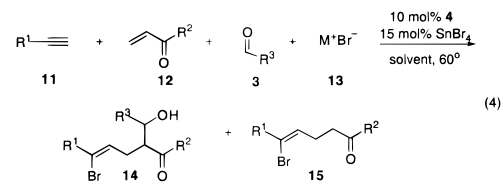
10.1021/ja001656v CCC: $19.00 
Published on Web 08/06/2000

**Table 1.** Four-Component Coupling via *cis*-Bromoalkylation[a]

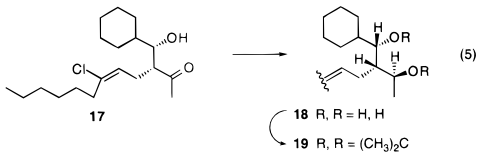
| entry | 3 | 11 ($R^{1)}$ | 12 ($R^{2)}$ | 13 | isolated yields 14 | isolated yields 15 | E:Z 14 | dr[b] |
|---|---|---|---|---|---|---|---|---|
| 1[c] | **3a** | *n*-$C_6H_{13}$ | $CH_3$ | LiBr | 60% | 20% | 1:1 | 1:1 |
| 2 | **3a** | *n*-$C_6H_{13}$ | $CH_3$ | **16** | 52% | 20% | 1:3.7 | >10:1[d] |
| 3 | **3b** | *n*-$C_6H_{13}$ | $CH_3$ | **16** | 55% | 18% | 1:5.7 | >10:1[d] |
| 4 | **3c** | *n*-$C_6H_{13}$ | $CH_3$ | **16** | 63% | 15% | 1:3.4 | 7:1 |
| 5 | **3d** | Ph | $CH_3$ | **16** | 40% | 11% | <2:>98 | 9:1 |
| 6 | **3a** | $NC(CH_2)_3$ | Ph | **16** | 46% | 15% | 1:4.4 | 8:1 |
| 7 | **3b** | $CH_3O_2C$-$(CH_2)_6$ | Ph | **16** | 59% | 11% | 1:3.1 | >10:1[d] |
| 8 | **3d** | $NC(CH_{2)3}$ | Ph | **16** | 70% | 15% | 1:5.5 | >10:1[d] |
| 9[e] | **3a** | *n*-$C_6H_{13}$ | $CH_3$ | **16** | 51% | 19% | 1:2.0 | >10:1[d] |

[a] All reactions run at 0.5 M in DMF as outlined in eq 4 unless noted otherwise. [b] Diastereomeric ratio of aldol adducts which is independent of alkene geometry. [c] Reaction performed in acetone. [d] Only one diastereomer seen for each alkene isomer by $^1$H NMR spectroscopy at 500 MHz. [e] Reaction performed at 0.5 M in acetone.

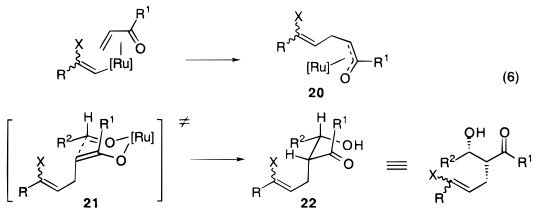



Utilizing our conditions for the three-component coupling (10% **4**, LiBr, at 0.5 M in acetone) but in the presence of an aldehyde gave a 60% yield of the desired four-component coupling product but, disappointingly, with no diastereoselectivity (entry 1). The striking contrast in diastereoselectivity with the chloroalkylation sequence, which gave only one diastereomer, could arise from the effect of the change in halide, in cation, or in solvent since the chloroalkylation reaction was performed in DMF with tetramethylammonium chloride. Changing the solvent to DMF led to a dilemma since the three-component bromoalkylation sequence gave very poor *E*:*Z* selectivity in this solvent. We therefore reexamined the bromoalkylation reaction in DMF. Changing the bromide source from lithium bromide to tetraethylammonium bromide improved the *E*:*Z* ratio to 1:2. Curiously, the use of the spirotetraalkylammonium bromide **16** gave the best *E*:*Z* selectivity (1:3) in DMF. As entry 2 illustrates, running the same four-component coupling in DMF with **16** as the bromide source gave a 52% yield of **14** as a 1:3.7 *E*:*Z* ratio wherein only a single diastereomer of each was detected by 500 MHz $^1$H NMR spectroscopy. Use of an aliphatic aldehyde gave good results also (entry 3). Like in the *trans*-chlororuthenation process, the *cis*-bromoruthenation version also showed excellent chemoselectivity in using an $\alpha,\beta$-unsaturated aldehyde as the carbonyl component (entry 4). With phenylacetylene, only the *Z* alkene isomer was isolated as a single diastereomer (entry 5). The reaction also gave somewhat improved *E*:*Z* ratios favoring the *Z*-isomer with 5-hexynonitrile (entries 6 and 8). Alternatively, using the spirotetraalkylammonium salt **16** in acetone also gave only a single aldol diastereomer for the initial reaction but in a somewhat lower *E*:*Z* ratio (entry 9).




In all cases, excellent diastereoselectivity for the aldol step was observed.[9,10] The relative stereochemistry of the aldol product as syn was established in the case of **17**. Diastereoselective reduction with triacetoxyborohydride[11] followed by acetonide formation gave an acetonide **19** consistent with the structure depicted.[12] Thus, the *syn*-aldol geometry implies good selectivity in the migratory insertion of the vinyl ketone to form a *Z*-enolate **20**[13] which undergoes reaction via a typical Zimmerman−Traxler[14] transition state **21** to produce the *syn*-aldol product **22**. While




the total suppression of the three-component coupling product, which derived from a proton serving as the electrophile, remains a goal, the four-component coupling product can be obtained in synthetically useful yields (40−70% yields) especially considering how many bonds are being formed in a single step. The high syn selectivity in the ruthenium-catalyzed aldol reaction is also noteworthy.[10] The kinetically formed enolate is captured without loss of regioselectivity. The utility of ruthenium enolates[5,13] in aldol reactions clearly merits further investigations which are underway in these laboratories.

**Acknowledgment.** We thank the National Institutes of Health, General Medical Sciences, and the National Science Foundation for their generous support of our work. A.B.P. has received an ACS Organic Division fellowship sponsored by Bristol Myers Squibb. Mass spectra were provided by the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

**Supporting Information Available:** An Appendix containing experimental details and results (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For an overview of the aldol reaction, see: Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapters 1.5 and 1.6.

(10) For generation and use of rhodium enolates in aldol reactions, see: Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938. Reetz, M. T.; Vougioukas, A. E. *Tetrahedron Lett.* **1987**, *28*, 793. Sato, S.; Matsuda, I.; Izumi, Y. *Tetrahedron Lett.* **1986**, *27*, 5517. For Pd and Pt, see: Fujimura, O. *J. Am. Chem. Soc.* **1998**, *120*, 10032. Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2747. Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648.

(11) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(12) See Supporting Information. A similar procedure giving the same relative stereochemistry was peformed for the product (**14**) from entry 3, Table 1.

(13) Transmetalation of the Ru enolate to form a tin enolate prior to the aldol reaction cannot be ruled out.

(14) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.