J|A|C|S COMMUNICATIONS

Published on Web 09/28/2009

Enantioselective Rhodium-Catalyzed Conjugate Alkynylation of 5-Benzylidene Meldrum's Acids with TMS-acetylene

Eric Fillion* and Alexander K. Zorzitto

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

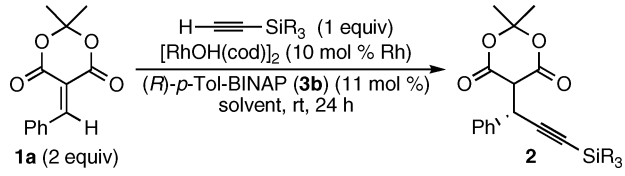
Received June 29, 2009; E-mail: efillion@uwaterloo.ca

Catalytic enantioselective conjugate alkynylation of electron-deficient olefins has recently attracted attention because of its synthetic utility.[1] To date, only four methods for carrying out this C−C bond-forming transformation have been disclosed: two used metalated terminal alkynes[2] and two in situ-generated metal alkynylides. From a practical point of view, the conjugate addition of in situ-generated metal alkynylides is of great interest, as it is accomplished in a single synthetic operation. In this context, Carreira and co-workers described the PINAP-catalyzed conjugate addition of in situ-generated copper aryl alkynylides to alkylidene Meldrum's acids.[3,4] The method was optimal for the conjugate addition of aryl acetylenes to alkylidene Meldrum's acids derived from aliphatic aldehydes.[1] Subsequently, the Rh-catalyzed asymmetric conjugate alkynylation of acyclic and cyclic enones using sterically shielded (triisopropylsilyl)acetylene[5] and analogous alkynylsilanols[6] in the presence of the chiral bisphosphine DTBM-SEGPHOS (**3a**) was reported by the Hayashi group.[7]

Herein, we present a method for the enantioselective conjugate addition of TMS-acetylene to benzylidene Meldrum's acids **1** catalyzed by a Rh(I) complex. It was postulated that as an alternative to the use of sterically shielded acetylenes to avoid competing terminal alkyne dimerization, highly electrophilic acceptors[8] would modify the kinetics of the process and favor this unprecedented conjugate alkynylation.

This hypothesis was verified by initially studying the addition of a series of silylated acetylenes to benzylidene Meldrum's acid **1a**. As depicted in Table 1, with $[RhOH(cod)]_2$ (10 mol % Rh), and (*R*)-*p*-Tol-BINAP (**3b**) (11 mol %), the silylacetylene addition proceeded at room temperature; the highest levels of conversion of **1a** to (*S*)-**2** were obtained with TMS-acetylene (entries 1, 4, 7, and 10). In addition, DME was found to be optimal in regard to conversion and enantioselectivity (entry 7).

Table 1. Influence of the Solvent and Silylacetylene

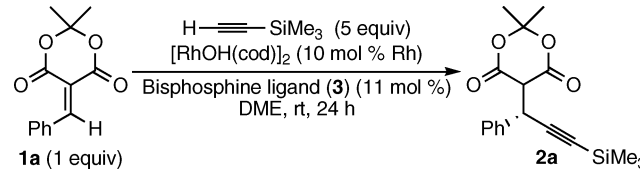


entry	solvent[a]	SiR_3	conversion (%)[b]	ee (%)
1	PhMe	$SiMe_3$	39 (**2a**)	78
2	PhMe	$SiMe_2{}^tBu$	23 (**2a′**)	69
3	PhMe	Si^iPr_3	15 (**2a″**)	14
4	THF	$SiMe_3$	41(**2a**)	66
5	THF	$SiMe_2{}^tBu$	26 (**2a′**)	62
6	THF	Si^iPr_3	23 (**2a″**)	3
7	DME	$SiMe_3$	54 (**2a**)	87
8	DME	$SiMe_2{}^tBu$	23 (**2a′**)	73
9	DME	Si^iPr_3	NR	−
10	1,4-dioxane	$SiMe_3$	30 (**2a**)	67
11	1,4-dioxane	$SiMe_2{}^tBu$	23 (**2a′**)	66
12	1,4-dioxane	Si^iPr_3	20 (**2a″**)	38

[a] The final concentration of silylacetylene was 0.6 M. [b] Determined by analysis of the ^1H NMR spectra of the crude reaction mixtures using mesitylene as internal standard.

With this promising lead in hand, we proceeded to optimize the reaction conditions to improve the conversion and enantioselectivity. For practical reasons and ease of purification of **2a**, benzylidene Meldrum's acid **1a** was used as the limiting reagent, with a 5-fold excess of TMS-acetylene. Under these conditions, $[RhOH(cod)]_2$ (10 mol % Rh)/**3b** (11 mol %) led to 62% conversion of **1a** to (*S*)-**2a**. The enantioselectivity was unaffected, as **2a** was obtained in 87% ee (Table 2, entry 1). Further optimization was realized by varying the chiral phosphine ligand.[9] (*R*)-3,5-Xylyl-BINAP (entry 2) provided similar results, while poor conversion was obtained with (*R*)-BINAP (entry 3). No conversion was observed with trialkylphosphine (entries 4−5) or monophosphine ligands (entries 6−8). (*R*)-DTBM-SEGPHOS (**3a**) furnished 85% conversion of **1a** to (*S*)-**2a** in 88% ee (entry 9). The series of (*S*)-MeO-BIPHEP ligands **3j**−**m** was then explored (entries 10−13); 3,5-Xylyl-MeOBIPHEP (**3m**) provided superior results, yielding (*R*)-**2a** in 94% ee at 70% conversion of **1a**.

Table 2. Survey of Chiral Phosphine Ligands



entry	ligand **3**	conversion (%)[a,b]	ee (%)
1	(*R*)-*p*-Tol-BINAP (**3b**)	62	87
2	(*R*)-3,5-Xylyl-BINAP (**3c**)	71	86
3	(*R*)-BINAP (**3d**)	25	N/A
4	(*R*,*R*)-Me-BPE (**3e**)	none	−
5	(*S*,*S*,*R*,*R*)-TangPHOS (**3f**)	none	−
6	(*R*,*R*)-BozPHOS (**3g**)	none	−
7	(*S*)-MOP (**3h**)	none	−
8	(*R*)-^{i}Pr-PHOX (**3i**)	none	−
9	(*R*)-DTBM-SEGPHOS (**3a**)	85	88
10	(*S*)-3,5-^{t}Bu-4-MeO-MeOBIPHEP (**3j**)	none	−
11	(*S*)-MeOBIPHEP (**3k**)	50[c]	83
12	(*S*)-*p*-Tol-MeOBIPHEP (**3l**)	66[c]	88
13	(*S*)-3,5-Xylyl-MeOBIPHEP (**3m**)	70[c]	94

[a] The final concentration of Meldrum's acid **1a** was 0.6 M. [b] Determined by analysis of the ^1H NMR spectra of the crude reaction mixtures. [c] (*R*)-**2a** was obtained.

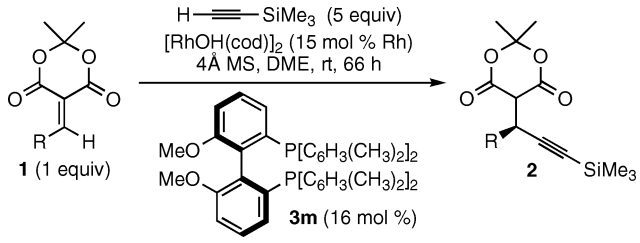
The alkynylation proceeded to completion when the catalyst loading was increased to 15 mol % Rh, which also benefited enantioselection. In the presence of **3m** (16 mol %) and $[RhOH(cod)]_2$ (15 mol % Rh), addition of TMS-acetylene to **1a** gave (*R*)-**2a** in 98% ee and 91% isolated yield after 66 h at room temperature (Table 3, entry 1).[10]

The scope of the catalytic conjugate alkynylation reaction was then explored, and the results are summarized in Table 3. 2-Naphthyl

10.1021/ja905336p CCC: $40.75

substrate **1b** provided **2b** in 99% ee (entry 2). Alkylidene **1c** reacted smoothly with TMS-acetylene, but a lower enantioselectivity was observed (entry 3). Substrate **1d** bearing a methyl group at the 2-position of the aromatic moiety withstood alkynylation (entry 4). The lower conversion of **1b** and the lack of reactivity of **1d** are likely the results of increased steric hindrance around the electrophilic carbon center. Methyl substitution at the 3- and 4-positions of the phenyl moiety had no impact on the enantioselectivity of the alkynylation (entries 5 and 6), but lower conversion was observed for para-substituted substrate **1f**. However, introduction of a larger alkyl group at the para position restored the reactivity: **1g** yielded **2g** in 94% ee (entry 7). A similar trend was observed with methoxy-substituted substrates **1h** and **1i**, as the 4-methoxy substrate was less reactive (entries 8 and 9). Replacing the methyl protecting group on the phenol with a pivalate group solved this reactivity issue. As a result, **1j** and **1k** furnished **2j** and **2k**, respectively, in good yields and ee's (entries 10 and 11). Methyl esters at the 3- and 4-positions of the arene also furnished the corresponding alkynylated products (entries 12 and 13). It was further shown that a range of functional groups, including triisopropylsilyl ether and free phenol (entries 14 and 15), was compatible with the conjugate alkynylation method. Furthermore, the mildness of the reaction conditions was clearly illustrated with boronic ester-substituted **1p**, which was stable and yielded **2p** in good yield and enantioselectivity (entry 16).

Table 3. TMS-acetylene Addition to Benzylidene Meldrum's Acids **1**



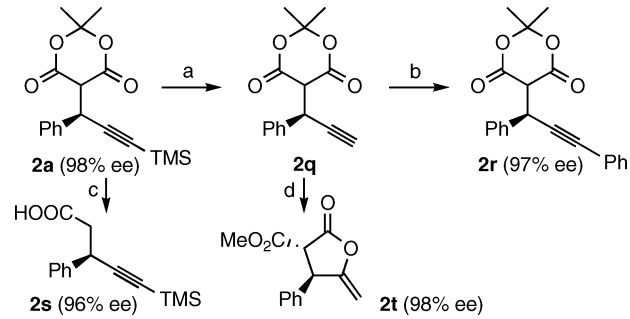
entry	R[a]	conversion (%)[b]	yield (%)	ee (%)
1	Ph (**1a**)	>95	91 (**2a**)	98
2	2-naphthyl (**1b**)	80	70 (**2b**)	99
3	^{i}Pr (**1c**)	>95	85 (**2c**)	74
4	2-MeC$_6$H$_4$ (**1d**)	NR	—	—
5	3-MeC$_6$H$_4$ (**1e**)	90	72 (**2e**)	98
6	4-MeC$_6$H$_4$ (**1f**)	73	65 (**2f**)	98
7	4-^{t}BuC$_6$H$_4$ (**1g**)	>95	73 (**2g**)	94
8	3-MeOC$_6$H$_4$ (**1h**)	>98	83 (**2h**)	95
9	4-MeOC$_6$H$_4$ (**1i**)	40	N/A	N/A
10	3-(OCO^{t}Bu)C$_6$H$_4$ (**1j**)	>98	83 (**2j**)	94
11	4-(OCO^{t}Bu)C$_6$H$_4$ (**1k**)	>98	86 (**2k**)	93
12	3-(CO$_2$CH$_3$)C$_6$H$_4$ (**1l**)	>95	74 (**2l**)	84
13	4-(CO$_2$CH$_3$)C$_6$H$_4$ (**1m**)	>95	80 (**2m**)	85
14	3-(TiPSO)C$_6$H$_4$ (**1n**)	>98	77 (**2n**)	89
15	3-(HO)C$_6$H$_4$ (**1o**)	>98	85 (**2o**)	97
16	3-[B(O$_2$C$_6$H$_{12}$)]C$_6$H$_4$ (**1p**)	>98	84 (**2p**)	92

[a] The final concentration of Meldrum's acid **1** was 0.6 M. [b] Determined by analysis of the ^{1}H NMR spectra of the crude reaction mixtures.

Starting from orthogonally functionalized **2a**, subsequent transformations generated diverse chiral structures without loss of enantiopurity. Deprotection of **2a** followed by Sonogashira coupling of the resulting terminal alkyne **2q** with iodobenzene provided **2r**.[11] Selective hydrolysis of the Meldrum's acid moiety of **2a** furnished carboxylic acid **2s**.[12] Lactone **2t** was formed by Ag_2CO_3-catalyzed heterocyclization of **2q**.

In conclusion, we have described a novel method for the enantioselective conjugate alkynylation of benzylidene Meldrum's acids using TMS-acetylene. This method employs the commercially available ligand 3,5-Xylyl-MeOBIPHEP (**3m**), and the mild reaction conditions are compatible with an array of functional groups. Further efforts to expand the scope of the enantioselective conjugate alkynylation of highly electrophilic acceptors with TMS-acetylene and to synthesize medicinally relevant compounds are underway.

Scheme 1. Synthetic Transformations of **2a**[a]



[a] Reagents and Conditions: (a) TBAF, THF, rt, 2 h, 83%; (b) PhI, CuI (29 mol %), $Pd_2(dba)_3$ (2.4 mol %), PhOH (2 equiv), nBu$_4$NI (2 equiv), DMF/^{i}Pr$_2$NEt (20:1), −5 °C, 1 h, 64%; (c) H_2O/pyridine (3:1), 95 °C, 4 h, 96%; (d) Ag_2CO_3 (10 mol %), PhH/MeOH (4:1), 85 °C, 2 h, 72%.

Acknowledgment. This work was supported by the Government of Ontario (Early Researcher Award to E.F.), the Merck Frosst Center for Therapeutic Research, NSERC, CFI, OIT, and the University of Waterloo. Aaron M. Dumas, University of Waterloo, is acknowledged for generously sharing benzylidene Meldrum's acids. Ashraf Wilsily, University of Waterloo, is thanked for help with the derivatization experiments.

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

References

(1) For a review, see: Fujimori, S.; Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Boyall, D.; Carreira, E. M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635.
(2) Conjugate addition of alkynyl boronates to β-aryl enones catalyzed by 3,3′-diiodobinaphthol: (a) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244. Stoichiometric conjugate addition of alkynyl boronates: (b) Chong, J. M.; Shen, L.; Taylor, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 1822. Chiral nickel−bisoxazoline complex-catalyzed conjugate addition of dimethylaluminum TMS-acetylide to 2-cyclohexenone: (c) Kwak, Y.-S.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3385. Me$_2$Zn- and chiral amino alcohol-mediated addition of aryl alkynes to nitro olefins under stoichiometric conditions: (d) Yamashita, M.; Yamada, K.; Tomioka, K. *Org. Lett.* **2005**, *7*, 2369. Organocatalytic formal alkynylation of α,β-unsaturated aldehydes: (e) Nielsen, M.; Jacobsen, C. B.; Paixão, M. W.; Holub, N.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 10581.
(3) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682.
(4) (a) Fujimori, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4964. (b) Knöpfel, T. F.; Boyall, D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2281. (c) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054.
(5) Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576.
(6) Nishimura, T.; Tokuji, S.; Sawano, T.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3222.
(7) Rh-catalyzed asymmetric rearrangement of alkynyl alkenyl carbinols, the synthetic equivalent of asymmetric conjugate alkynylation of enones, has been reported. See: Nishimura, T.; Katoh, T.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14158.
(8) Highly electrophilic alkylidene Meldrum's acids have been shown to participate in various conjugate additions under mild reaction conditions. See: (a) Wilsily, A.; Lou, T.; Fillion, E. *Synthesis* **2009**, 2066. (b) Dumas, A. M.; Fillion, E. *Org. Lett.* **2009**, *11*, 1919. (c) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801. (d) Fillion, E.; Carret, S.; Mercier, L. G.; Trépanier, V. É. *Org. Lett.* **2008**, *10*, 437. (e) Fillion, E.; Wilsily, A.; Liao, E-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957. (f) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774.
(9) For a complete survey of ligands, see the Supporting Information.
(10) The addition of 4 Å molecular sieves provided consistent yields and ee's.
(11) The absolute stereochemistry of the addition products was determined by comparison with known compound **2r** (see ref 3).
(12) 3-Substituted phenylpropionic acid is a salient structural motif in medicinal chemistry. See: Bharate, S. B.; Nemmani, K. V. S.; Vishwakarma, R. A. *Expert Opin. Ther. Pat.* **2009**, *19*, 237.

JA905336P