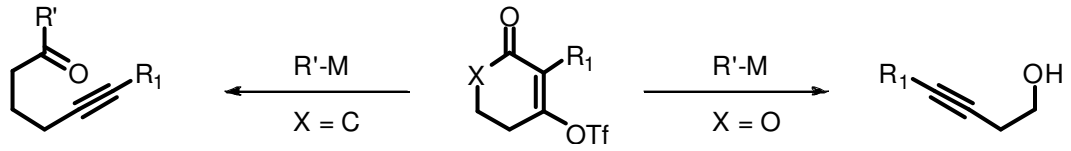
Ring Opening/Fragmentation of Dihydropyrones for the Synthesis of Homopropargyl Alcohols



Jumreang Tummatorn and Gregory B. Dudley

J. Am. Chem. Soc. 2008, ASAP

Current Literature Presentation

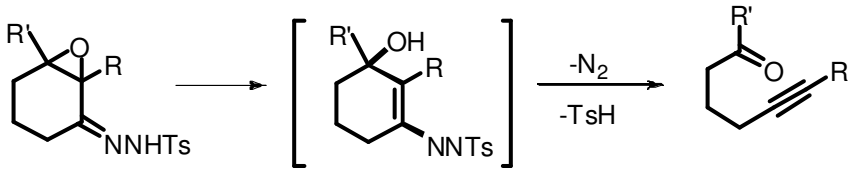
Abhisek Banerjee

Wipf Group

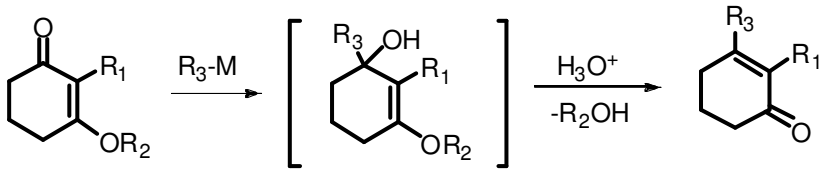
Mar-29-2008

The Crossover Reaction

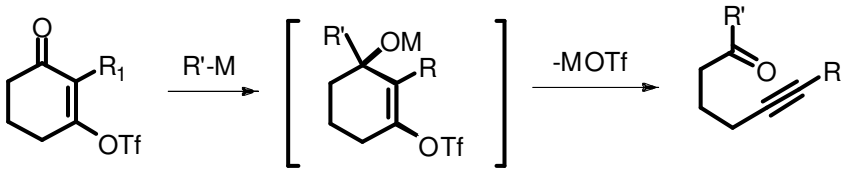
The Eschenmoser-Tanabe Fragmentation



Enone Formation from Vinylogous Acid Ester

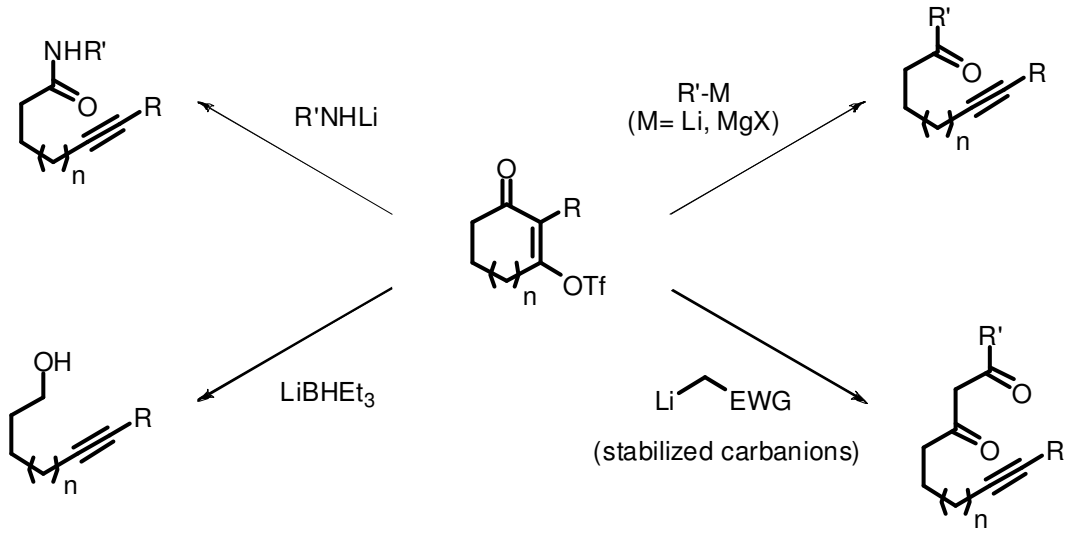


Tandem Addition/Fragmentation of Vinylogous Acyl Triflates



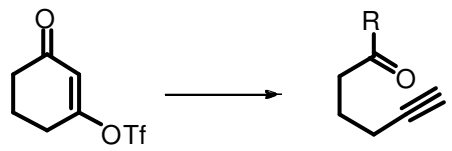
Dudley et al. *J. Am. Chem. Soc*. **2006**, *128*, 6499

Tandem Nucleophilic Addition/C-C Bond Fragmentation Reactions of Vinylogous Acyl Triflates

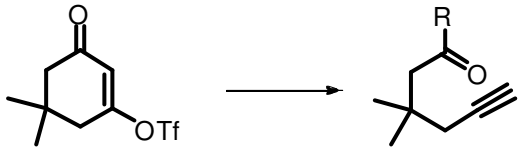


Dudley et al. *J. Am. Chem. Soc*. **2006**, *128*, 6499

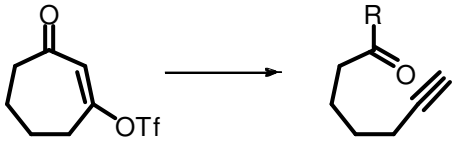
Synthesis of Acetylene tethered Ketones



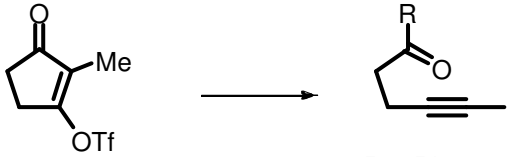
R = Ph, 65%
R = Bu, 63%



R = Ph, 96%
R = Bu, 52%



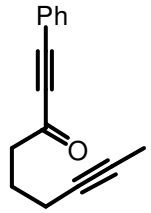
R = Ph, 79%
R = Bu, 39%



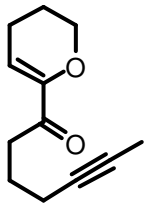
R = Ph, 61%
R = Bu, 14%

Reaction Conditions: Vinylogous acyl triflate (0.55 mmol), RLi (0.50 mmol) in solvent (2 mL)
R = Ph, THF; R = n-Bu, Toluene

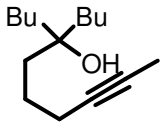
- Other Aryl Grignard or Lithium reagent such as *o*-, *m*-, *p*-$(MeO)C_6H_4$-MgBr.
- Other Alkyl Lithium reagent such as *i*-PrLi, *t*-BuLi, MeLi.
- Yields suffer with reactive and hindered nucleophilic reagents.



56%
alkynyl lithium reagent



64%
vinyl lithium reagent



77%
excess lithium reagent
(2.2 equiv.)

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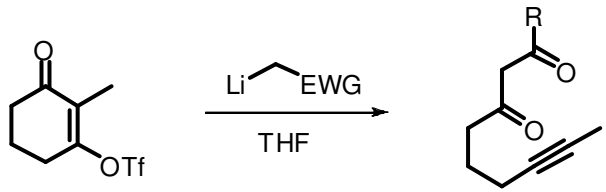
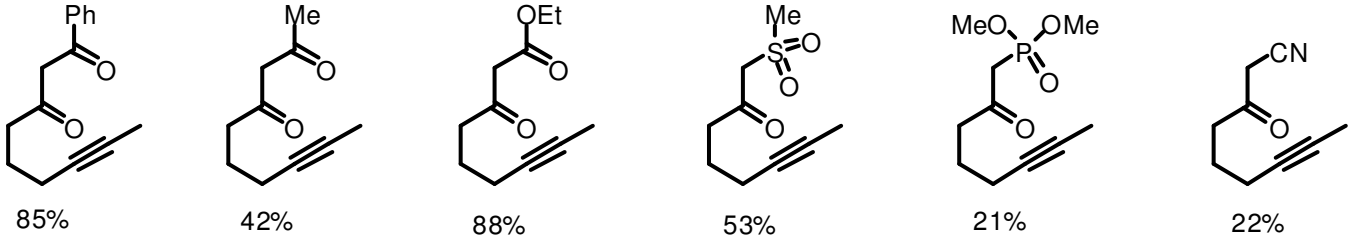
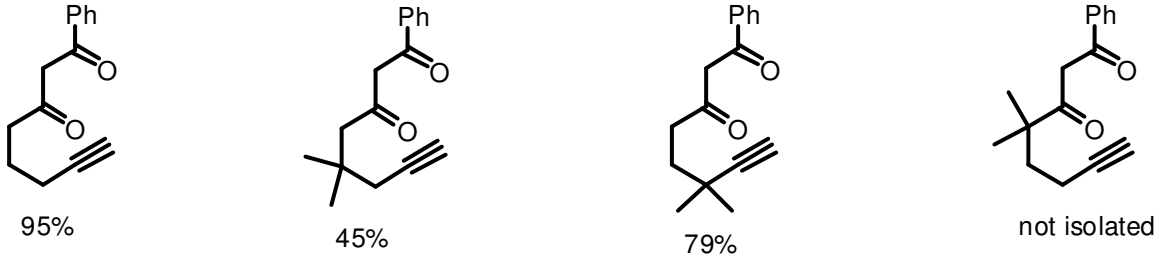
Synthesis of Acetylene tethered 1,3-Diketones



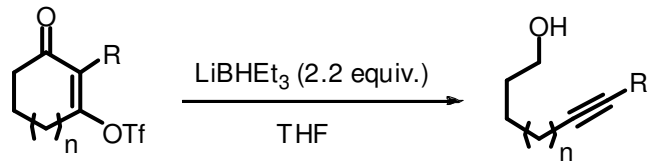
Stoichiometry: Triflate (1 equiv.); Prenucleophile (2.6 equiv.), LiHMDS (2.2 equiv.)

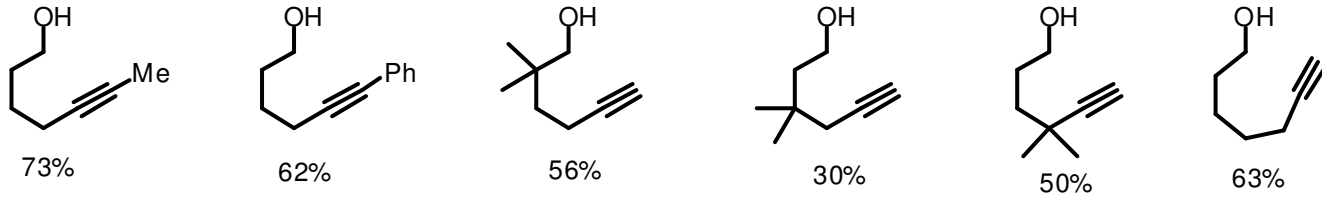




Dudley et al. *J. Am. Chem. Soc*. **2006**, *128*, 6499

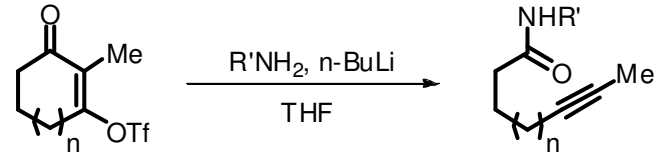
Synthesis of Acetylene tethered Alcohols

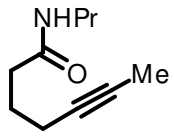




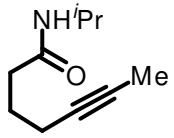
Dudley et al. *J. Am. Chem. Soc*. **2006**, *128*, 6499

Synthesis of Acetylene tethered Amides

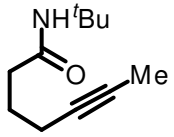




91%



87%



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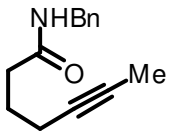

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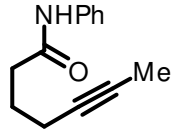

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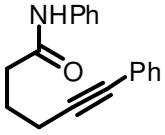
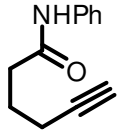
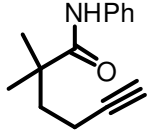


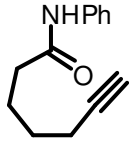
84%



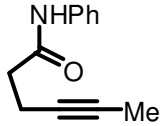
59%



<7%



88%



20%

secondary amines resulted in decomposition of the triflate

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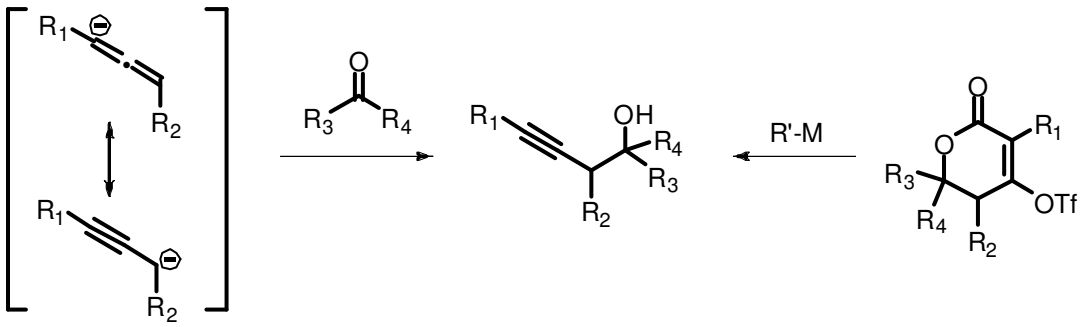
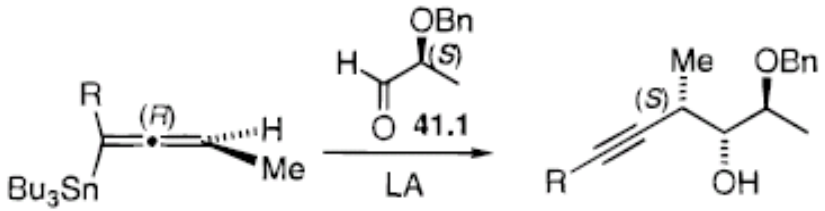
Synthesis of Homopropargyl Alcohols

Homopropargyl alcohols key building block for synthesis of Polyketides and macrolides





(*R*)-**60.1** R = CH_2CH_3 **61.1** *(syn)* R = CH_2CH_3

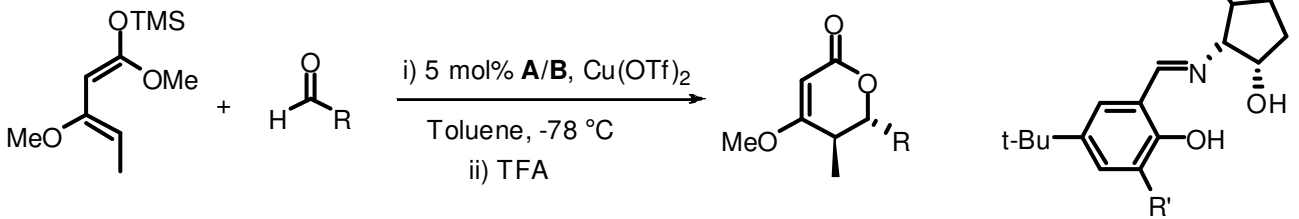
(*R*)-**60.2** R = CH_2OAc **61.2** *(syn)* R = CH_2OAc

R	LA	yield, %	*syn:anti*
CH_2CH_3	$BF_3•OEt_2$	89	>99:1
CH_2OAc	$BF_3•OEt_2$	97	97:3
CH_2CH_3	$MgBr_2•OEt_2$	95	1:99
CH_2OAc	$MgBr_2•OEt_2$	97	1:99

Marshall et al. *Chem. Rev*. **1996**, *96*, 31

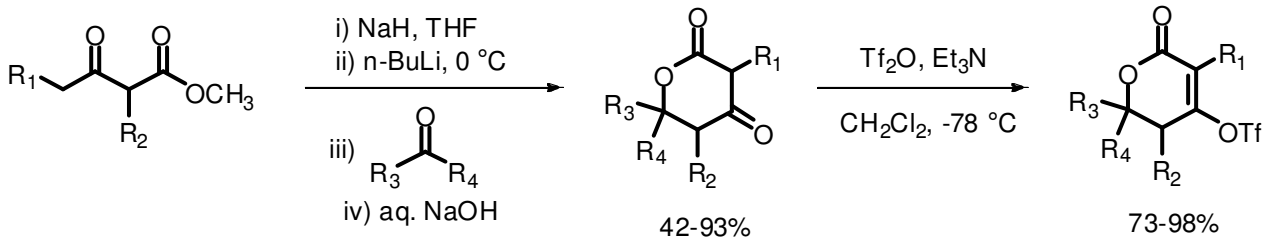
Synthesis of Chiral Dihydropyrones

Hetero Diels-Alder Approach:



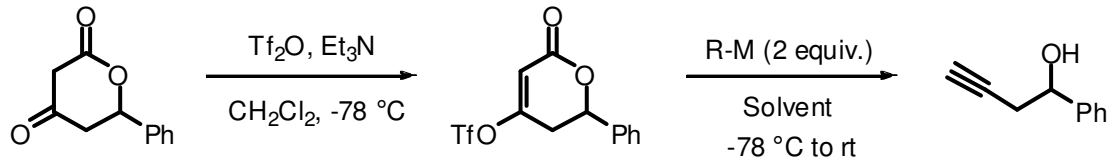
Feng et al. *J. Org. Chem*. **2006**, *71*, 4141

Author's Approach:



Imbroisi et al. *Bioorg. Med. Chem*. **2004**, *12*, 865

Decomposition of DHP Triflate Under Various Conditions



entry	R–M	solvent	yield
1[a]	Ph–Li[b]	THF	48%
2	Ph–MgBr[c]	THF	54%
3	Ph–MgBr[c]	toluene	84%
4	*p*-MeO–C_6H_4–MgBr[d]	toluene	51%
5	*n*-Bu–MgCl[e]	toluene	70%
6	**Me–MgBr[c]**	**toluene**	**>95%**
7	Me–Li[f]	toluene	42%
8	*i*-Pr–Li[g]	toluene	15%

[a] −78 °C → 60 °C. [b] 2.0 M in butyl ether. [c] 3.0 M in ether. [d] 0.5 M in THF. [e] 2.0 M in ether. [f] 1.6 M in ether. [g] 0.7 M in pentane.

- Toluene is better solvent than THF
- Grignard Nucleophiles outperformed organolithiums
- Methylmagnesium bromide is optimal choice

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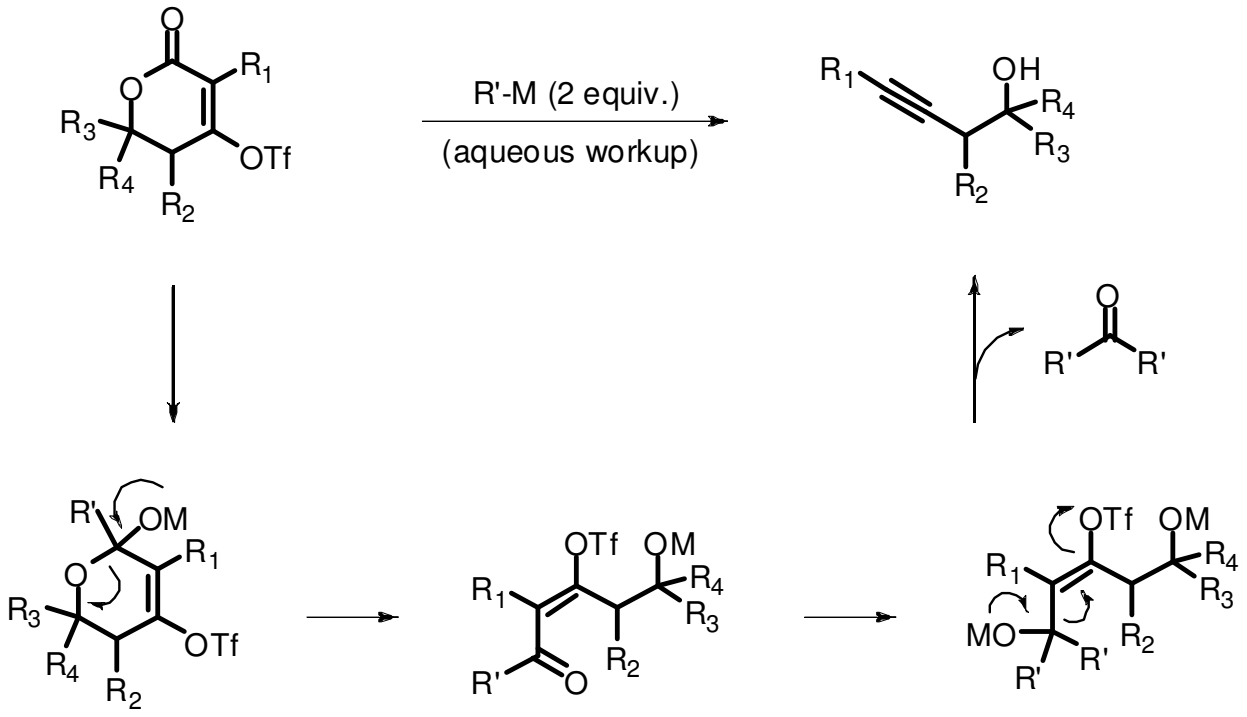
Postulated Reaction Pathway



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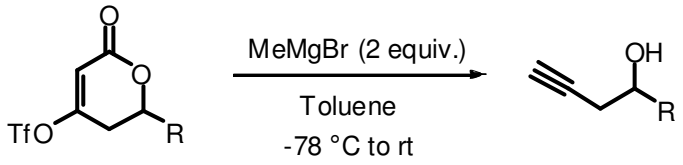
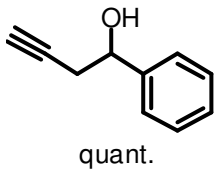
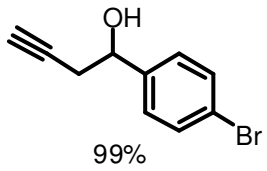
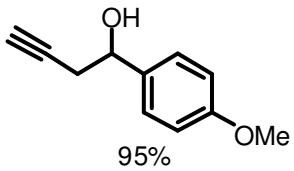
Decomposition of DHP Triflates with MeMgBr

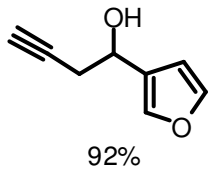


Aryl Substituents:



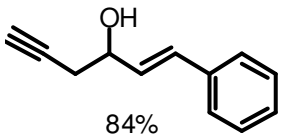


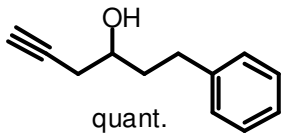


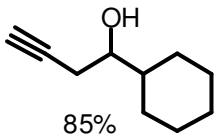


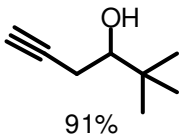
electron poor

electron rich









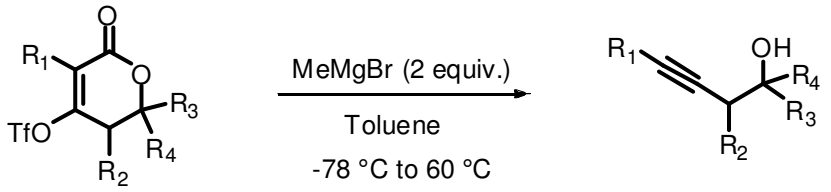
linear

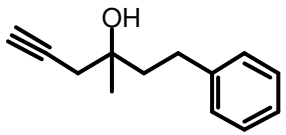
branched

tertiary

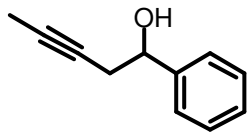
Dudley et al. *J. Am. Chem. Soc.* **2008**, *130*, ASAP

Decomposition of Substituted DHP Triflates

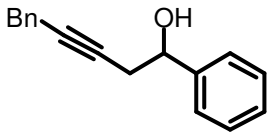




R_1= H; R_2 = H;
R_3 = $PhCH_2CH_2$; R_4 = Me, 82%



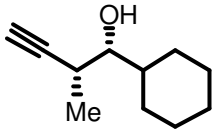
R_1= Me; R_2 = H;
R_3 = Ph; R_4 = H, quant.



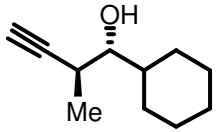
R_1= Bn; R_2 = H;
R_3 = Ph; R_4= H, 92%

geminal disubstitution, tertiary alcohol

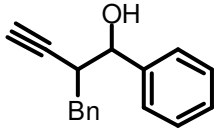
internal alkynes



R_1= H; R_2 = Me;
R_3 = Cy; R_4 = H, 76%



R_1= H; R_2 = Me;
R_3 = H; R_4 = Cy, 78%



R_1= H; R_2 = Bn;
R_3 = H; R_4 = Ph, 83%

cis DHP to *syn* HPA

trans DHP to *anti* HPA

Dudley et al. *J. Am. Chem. Soc*. **2008**, *130*, ASAP

Summary

✓C-C bond cleaving fragmentation reaction induced by the addition of various nucleophiles to cyclic vinylogous acyl triflates produces acyclic acetylenic compounds.

✓Nucleophilic addition of methylmagnesium bromide to 5,6-dihydro-2-pyrone (DHP) initiates a ring opening/fragmentation process to furnish homopropargyl alcohols.

✓This stereospecific strategy provides chiral homopropargyl alcohols that may be difficult to access by other means.