J|A|C|S COMMUNICATIONS

Published on Web 12/19/2008

Ruthenium-Catalyzed Cross-Coupling of Tertiary Propargyl Alcohols with ω-Alkynenitriles: A Regio- and Stereoselective Surrogate for an Aldol Condensation

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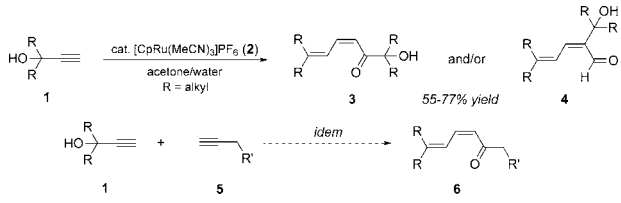
Received October 1, 2008; E-mail: bmtrost@stanford.edu

The aldol condensation is a well-recognized, powerful method for the elaboration of complexity through carbon−carbon bond formation.[1] Though the advent of organocatalytic processes made cross-aldol reactions more common and reliable, achieving the regioselective cross-aldol condensation of unsymmetrical ketones as aldol donors is still a difficult endeavor.[2]

Recent developments in organometallic chemistry have dealt with the selective activation of triple bonds in carbon−carbon and carbon−heteroatom bond-forming events. Alkynes are prone to undergo a host of chemoselective transformations that quickly build up complexity, such as reductive coupling reactions,[3] alkyne−alkene couplings,[4] or cycloadditions.[5]

Coupling reactions involving two or more separate (i.e., nontethered) alkyne entities, however, are much less frequent as they present a number of chemo- and regioselectivity challenges.[6] Interestingly, our laboratory has previously developed such a reaction in the form of a homocoupling of tertiary propargyl alcohols **1** (Scheme 1).[7,8] Upon exposure to the cationic ruthenium(II) complex $[CpRu(MeCN)_3]PF_6$ **2**, these compounds undergo an unusual, atom-economical conversion to dimeric hydroxydienones **3** (or hydroxydienals **4**). This remarkably facile reaction formally delivers compounds that can be viewed as cross-aldol products between an α-hydroxyketone and an enal. A mechanistic rationale was proposed which included metallacyclopentene formation, followed by water elimination and readdition at the ensuing carbene carbon.[8,9]

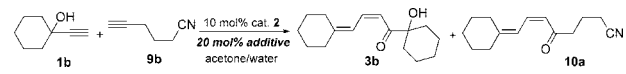
Scheme 1. Dimerization of Tertiary Propargyl Alcohols and Proposed Cross-Coupling with a Different Alkyne



Since only one molecule of propargyl alcohol should be necessary on the basis of this mechanism, our attention was piqued by the challenge of effecting an analogous *heterodimerization* (cross-coupling) under similar conditions. In such a blueprint, a molecule of propargyl alcohol **1** would be cross-coupled with a different alkyne partner **5**. Apart from the conceptual novelty of such a prospect, the final products **6** would be cross-aldol products formally derived from an unsymmetrical ketone, formed in a completely atom-economical manner. Given the inherent facility of homodimerization of the propargyl alcohol component, from the onset we were faced with the highly challenging task of diverting the reaction manifold leading to dimeric product. It was surmised that overcoming this daunting obstacle would most likely entail the choice of a functionalized alkyne partner, bearing a suitable coordinating moiety. In this Communication, we detail our findings on the unique ability of ω-cyanoalkynes to divert the dimerization of propargyl alcohols into a powerful alkyne−alkyne cross-coupling reaction manifold.

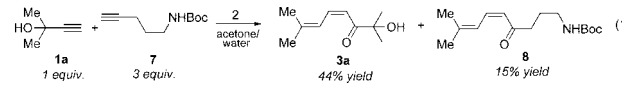
Bringing this plan to fruition was far from a trivial matter. For instance (eq 1), while the *tert*-butoxycarbonylaminoalkyne **7** did provide a low yield of the desired cross-coupled adduct **8** upon treatment with 2-methyl-2-butynol **1a** and a catalytic amount of ruthenium complex **2**, significant amounts (>40% yield) of the dimeric hydroxydienone **3a** were still obtained under these conditions. Other terminal alkynes bearing polar groups (e.g., −OH, −COOH, oxime, −OAc, phthalimide) did not provide better results.[10]

Table 1. Optimization of the Acid Cocatalyst in the Cross-Coupling of **1b** with **9b**



entry	additive	ratio 10a/3b	yield[a,b]
1	none	5:1	40%
2	malonic acid	5:1	50%
3	oxalic acid	5:1	52%[c]
4	**tartaric acid**	**5:1**	**70%**
5	salicylic acid	4:1	70%
6	phthalic acid	4:1	67%
7	chloroacetic acid	3.3:1	58%

[a] All reactions carried out at room temperature with 3 equiv of **9b** and 1 equiv of **1b**. [b] Yields refer to for pure, isolated products. [c] Isolated as a 1.2:1 mixture of *E*/*Z* isomers.



(1)

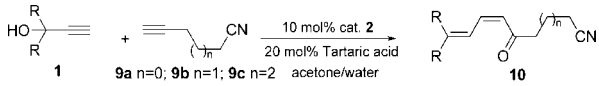
A significant breakthrough was achieved when ω-alkynylnitrile **9b** was employed (Table 1). In spite of a low yield of the cross-coupled product **10a** in initial attempts, considerably smaller amounts of the homodimer **3b** were obtained, suggesting that the nitrile partner was exquisitely effective in its ability to disrupt the facile dimerization pathway reported above. We thus decided to study this reaction in greater detail, and in the course of optimization studies became aware of the pronounced effect that acidic additives have on this process. Table 1 displays selected results obtained for carboxylic acid additives.[11]

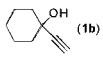
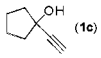
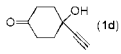
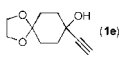
As portrayed in the table, the nature of the carboxylic acid cocatalyst has a dramatic impact on the yield and selectivity of this reaction. In particular, it appears that dicarboxylic acids or monoderivatives bearing a potential coordinating site have a benign effect on the cross-coupling yield, and among these there is a slight proportionality effect with the pK_a value (cf. Table 1, entries 2, and 4−6 and the pK_a values: malonic acid, 2.86; phthalic acid, 2.95; salicylic acid, 2.97; tartaric acid, 3.03).[12] The best results were obtained with D-tartaric acid.

With a suitable catalytic system in hand, we then set to examine the scope of this novel transformation. Our results are compiled in Table 2. It is interesting to note that all the propargyl alcohols examined had been shown to successfully undergo homodimerization in our previous study.[7] Nonetheless, in most of the cases studied here, less than 10% of the corresponding dimers have been isolated, with the cross-coupling manifold predominating in every instance. Remarkably, these reactions take place at room temperature in less than 8 h under the mildest of conditions. The functional group tolerance of the process

10.1021/ja8077686 CCC: $40.75

Table 2. Ruthenium-Catalyzed Cross-Coupling of Tertiary Propargyl Alcohols with ω-Cyanoalkynes

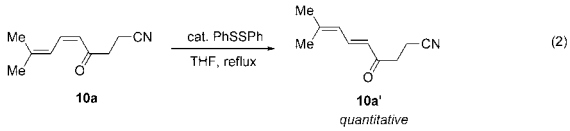


Entry	R	Nitrile	Product	Yield[a,b]
1	Me (**1a**)	**9a**	**10a**	65%
2		**9b**	**10b**	69%
3		**9c**	**10c**	75%
4	 (**1b**)	**9b**	**10d**	70%
5		**9c**	**10e**	68%
6	 (**1c**)	**9a**	**10f**	60%
7		**9c**	**10g**	52% (63)
8	 (**1d**)	**9b**	**10h**	68%
9	 (**1e**)	**9a**	**10i**	50% (62)
10		**9c**	**10j**	63%

[a] All reactions carried out at room temperature (4−8 h) with 3 equiv of **9** and 1 equiv of **1**. [b] Yields refer to pure, isolated products. Yields between brackets are based on recovered, unreacted propargyl alcohol. For details on the amounts of dimer **3** isolated, see the Supporting Information.

also appears to be broad, allowing the presence of free carbonyl groups and acetals (Table 1, entries 8−10). Importantly, the length of the nitrile tether can also be varied to considerable extent (**9a**−**9c**), indicating that there is some flexibility in the coordination mode of the cyano-partner to the metal center.[13]

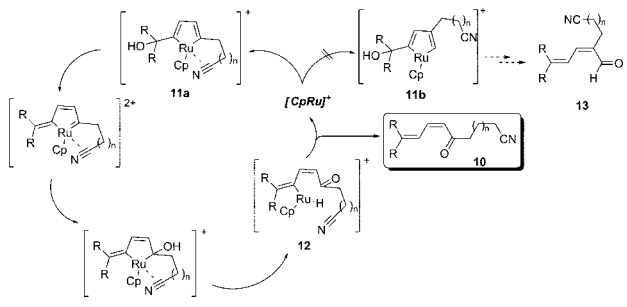
Furthermore, in all obtained products the α,β-unsaturated moiety is exclusively *Z*-configured (to the limit of detection by NMR), an observation with important implications in mechanistic terms (vide infra). On the other hand, smooth and quantitative (*Z*)- to (*E*)-isomerization can be brought about by brief exposure of the products to catalytic PhSSPh in refluxing THF, thus providing easy access to both double-bond stereoisomers at will (eq 2).



(2)

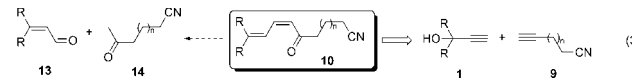
Our working mechanistic rationale for this catalytic, atom-economical process is depicted in Scheme 2.[7−9] Of the two possible nonsymmetric ruthenacyclopentadienes that can be formed, the 2,5-disubstituted isomer **11a** is likely to be favored because of the possibility of chelation by the cyano substituent. The alternative isomer **11b**, which would lead to an aldehyde cross-coupled product

Scheme 2. Mechanistic Proposal for the Cross-Coupling Reaction



(**13**, not observed), is either not formed or exists in rapid equilibrium with its prefered congener **11a**.

In summary, we have developed an unprecedented, atom-economical[14] ruthenium-catalyzed alkyne−alkyne cross coupling between cyanoalkynes and propargyl alcohols. It provides an interesting example of the uniqueness of the cyano group in the context of coordination to metal fragments, while delivering highly functionalized, stereodefined dienylketones. Moreover, this reaction can be considered as a chemoselective, atom-economical surrogate for the aldol condensation (eq 3) as the products are formally derived from a vinylaldehyde **13** and an unsubstituted methyl ketone **14**; that the thermodynamically less stable, (*Z*)-double bond isomer is selectively produced only further emphasizes the unusual character of this process, as such a direct reaction is not feasible with the currently available aldol technology.[15] Importantly, since quantitative isomerization to the (*E*)-counterpart can be easily achieved, stereoselective access to both isomers *at will* is gained.



(3)

Acknowledgment. We thank the National Science Foundation for their generous support of our programs. N.M. is grateful to the Fundação para a Ciência e Tecnologia (FCT) for the awarding of a Postdoctoral fellowship. We thank Johnson-Matthey for a generous gift of ruthenium complexes.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) See: (a) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem.—Eur. J.* **2002**, *8*, 36–44.
(2) For selected reviews: (a) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293. (b) List, B. *Tetrahedron* **2002**, *58*, 5573–5590.
(3) (a) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653–661. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467–473.
(4) (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067–2096. (b) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16.
(5) (a) Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1–8. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92. (c) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2915.
(6) For instance, the extensive body of work done on the [2+2+2] cyclotrimerization of alkynes shows that, in general, regioselectivity can only be reliably achieved when two of the alkyne partners are tethered. See: (a) Maitlis, P. M. *Acc. Chem. Res.* **1976**, *9*, 93–9, and ref 3 For an example of in situ-tethering, see: (b) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625–9631.
(7) (a) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2001**, *123*, 8862–8863.
(8) For other examples of alkyne dimerization processes, see: (a) Le Paih, J.; Derien, S.; Demerseman, B.; Bruneau, C.; Dixneuf, P. H.; Toupet, L.; Dazinger, G.; Kirchner, K. *Chem.—Eur. J.* **2005**, *11*, 1312–1324. (b) Le Paih, J.; Monnier, F.; Derien, S.; Dixneuf, P. H.; Clot, E.; Eisenstein, O. *J. Am. Chem. Soc.* **2003**, *125*, 11964–11975. (c) Le Paih, J.; Derien, S.; Bruneau, C.; Demerseman, B.; Toupet, L.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2912–2915. (d) Le Paih, J.; Derien, S.; Dixneuf, P. H. *Chem. Commun.* **1999**, 1437–1438.
(9) For further development of cycloisomerizations based on the same principle, see: (a) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763–4776. (b) Trost, B. M.; Rudd, M. T.; Costa, M. G.; Lee, P. I.; Pomerantz, A. E. *Org. Lett.* **2004**, *6*, 4235–4238. (c) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 11516–11517. (d) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4178–4179.
(10) Slow addition of the propargyl alcohol component via syringe pump techniques or similar attempts at minimizing the effective concentration of the propargyl alcohol in solution did not provide significant improvement either.
(11) Other acid additives tested include trifluoroacetic acid, $CeCl_3$, and DABCO·2HPF$_6$.
(12) See http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.
(13) No dimerization of the cyanoalkyne was observed.
(14) Trost, B. M. *Science* **1991**, *254*, 1471–1477.
(15) For a surrogate to such a reaction, see: Nakamura, S.; Hayakawa, T.; Nishi, T.; Watanabe, Y.; Toru, T. *Tetrahedron* **2001**, 6703–6711.

JA8077686