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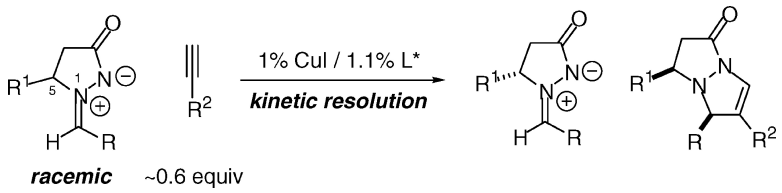
J. Am. Chem. Soc., **2005**, 127 (32), 11244-11245• DOI: 10.1021/ja052876h • Publication Date (Web): 21 July 2005



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Kinetic Resolutions of Azomethine Imines via Copper-Catalyzed [3 + 2] Cycloadditions

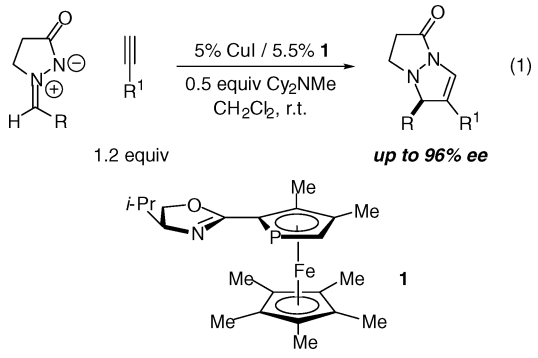
Andrés Suárez, C. Wade Downey, and Gregory C. Fu*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received May 2, 2005; E-mail: gcf@mit.edu

The kinetic resolution of racemic mixtures is a powerful method for preparing enantiomerically enriched compounds,[1,2] complementing approaches such as asymmetric synthesis and classical resolution. Of course, the use of a chiral catalyst, rather than a stoichiometric reagent, to effect the kinetic resolution can be advantageous from the standpoint of considerations such as cost and efficiency. To date, there are only scattered examples of kinetic resolutions that capitalize on a 1,3-dipolar cycloaddition as the key enantiomer-differentiating step;[3] to the best of our knowledge, none of these methods exploits a chiral catalyst.

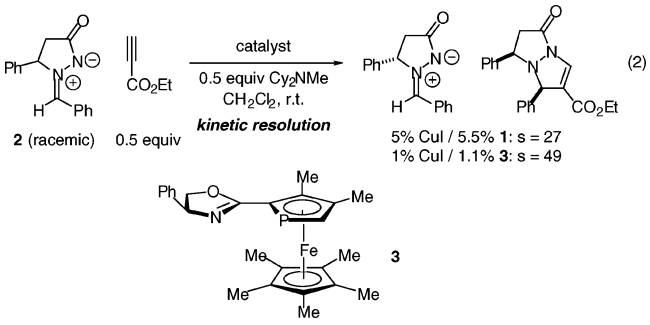
We recently described the development of a new copper-catalyzed reaction, the asymmetric [3 + 2] cycloaddition of azomethine imines with terminal alkynes (eq 1),[4] a process that likely involves reaction of the dipole with a copper acetylide generated in situ.[5] Our initial investigation focused on couplings of achiral azomethine imines with alkynes to furnish bicyclic pyrazolidinone derivatives, a family of molecules with interesting bioactivity.[6] More recently, we decided to explore the use of copper/phosphaferrocene−oxazoline catalysts for the kinetic resolution of racemic mixtures of azomethine imines; the resulting highly enantioenriched dipoles could then be reacted with nucleophiles or dipolarophiles to afford a wide array of useful monocyclic and bicyclic pyrazolidinones.[7,8]



(1)

For our initial studies, we chose to investigate the kinetic resolution of azomethine imine **2** (eq 2). We were pleased to discover that, under the conditions that we had previously described (eq 1), CuI/**1**-catalyzed cycloaddition with ethyl propiolate leads to effective kinetic resolution of the dipole (eq 2; s = selectivity factor = [rate of fast-reacting enantiomer/rate of slow-reacting enantiomer]). Upon surveying other ligands, we determined that phosphaferrocene−oxazoline **3** furnishes a selectivity factor higher than that of **1** and allows the use of a lower catalyst loading (eq 2).

We have examined the influence of the alkyne on the selectivity factor for these kinetic resolutions of azomethine imines (Table 1).[9] A variety of electron-poor alkynes provide useful selectivities



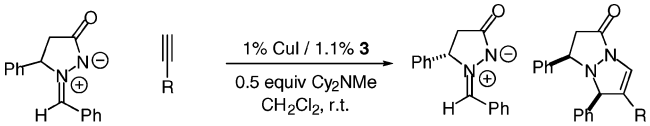
(2)

(s > 10),[10] with ethyl propiolate and 4-(trifluoromethyl)phenylacetylene being the most effective among those that we have explored to date (entries 1 and 3).

Next, we turned our attention to defining the scope of this new kinetic resolution process. As illustrated in Table 2, good selectivity factors are obtained for azomethine imines that possess a wide variety of N1 substituents. Thus, highly enantioenriched dipoles can be generated that bear aryl (entry 1), heteroaryl (entries 2 and 3), alkenyl (entry 4), and cycloalkyl (entry 5) groups.[11]

We have also examined the scope of this kinetic resolution with respect to substitution at the other two positions of the heterocycle (C4 and C5). Unfortunately, C4-substituted (e.g., cyclohexyl) azomethine imines do not undergo kinetic resolution with useful selectivity (s < 2). On the other hand, a variety of C5-substituted dipoles can be effectively resolved by CuI/**3** (Table 3). Thus, the 5 position can bear not only an aryl (entries 1 and 2) but also a heteroaryl (entry 3) or a branched alkyl (entries 4 and 5) group; the presence of an unbranched alkyl substituent leads to low selectivity (s < 5). As indicated in Table 3, in certain instances, we employ an amide- rather than an ester-substituted alkyne as the dipolarophile since side reactions are occasionally observed during cycloadditions of ethyl propiolate.[12]

Table 1. Kinetic Resolutions of Azomethine Imines: Dependence of the Selectivity Factor on the Structure of the Alkyne

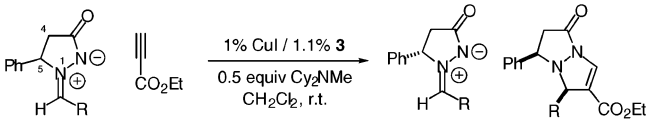


entry	R	s[a]	ee of the dipole (%) [isolated yield (%)]
1	CO_2Et	**53**	99 [42]
2	CONMePh	**30**	91 [42]
3	4-(trifluoromethyl)phenyl	**53**	99 [39]

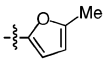
[a] The selectivity factors are the average of two experiments.

10.1021/ja052876h CCC: $30.25

Table 2. Kinetic Resolutions of Azomethine Imines: Variation of the N1 Substituent

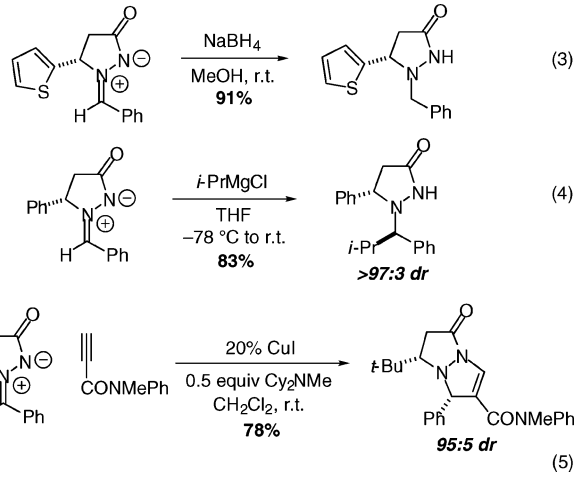


racemic 0.5-0.6 equiv

entry	R	s[a]	ee of the dipole (%) [isolated yield (%)]
1	Ph	**53**	99 [42]
2		**96**	95 [48]
3[b]		**27**	99 [31]
4		**35**	95 [36]
5	Cy	**15**	91 [36]

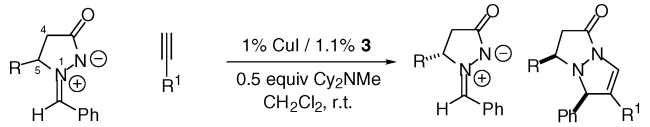
[a] The selectivity factors are the average of two experiments. [b] Solvent: $CHCl_3$.

The highly enantioenriched dipoles that are produced in these kinetic resolutions serve as precursors to useful families of compounds, such as monocyclic and bicyclic pyrazolidinones. A few examples are provided in eq 3−5.[13]



In summary, we have developed an effective method for the kinetic resolution of racemic azomethine imines via copper-catalyzed [3 + 2] cycloadditions with alkynes. The process tolerates a variety of N1 and C5 substituents on the dipole, thereby furnishing an array of useful enantioenriched azomethine imines. Additional investigations of copper-catalyzed cycloadditions are underway.

Table 3. Kinetic Resolutions of Azomethine Imines: Variation of the C5 Substituent



racemic 0.5-0.65 equiv

entry	R	R^1	s[a]	ee of the dipole (%) [isolated yield (%)]
1	Ph	CO_2Et	**53**	99 [42]
2[b,c]	3-bromophenyl	CONMePh	**54**	99 [44][d]
3[b]	2-thienyl	CO_2Et	**15**	98 [31]
4	*i*-Pr	CONMePh	**76**	97 [40][d]
5	*t*-Bu	CONMePh	**51**	93 [48]

[a] The selectivity factors are the average of two experiments. [b] Reaction temperature: 0 °C. [c] 2% CuI/2.2% **3**. [d] Yield of the pyrazolidinone after reduction of the dipole.

Acknowledgment. Support has been provided by the NIH (National Institute of General Medical Sciences: R01-GM66960), the Spanish Ministry of Education and Science (postdoctoral fellowship to A.S.), Merck Research Laboratories, and Novartis. Funding for the MIT Department of Chemistry Instrumentation Facility has been furnished in part by NSF CHE-9808061 and NSF DBI-9729592.

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

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(9) Notes: (a) Use of $CHCl_3$ (but not THF or EtOAc) leads to a comparable selectivity factor. (b) CuCl and CuBr can also be used. (c) The selectivity factor is not highly temperature-dependent.

(10) For a kinetic resolution that proceeds with a selectivity factor of 10, starting material of 90% ee can be obtained at 62% conversion.

(11) If R (Table 2) is an acyclic alkyl group (e.g., *i*-Bu), the dipole decomposes to a small extent during the cycloaddition, thereby precluding a reliable determination of the selectivity factor.

(12) Through X-ray crystallography, we have determined the absolute configuration of the recovered dipole from entry 2 of Table 3. The other configurations are assigned by analogy.

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JA052876H