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Expanding the Scope of Donor/Acceptor Carbenes to *N*-Phthalimido Donor Groups: Diastereoselective Synthesis of 1-Cyclopropane α-Amino Acids

Joshua S. Alford and Huw M. L. Davies*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322, United States

hmdavie@emory.edu

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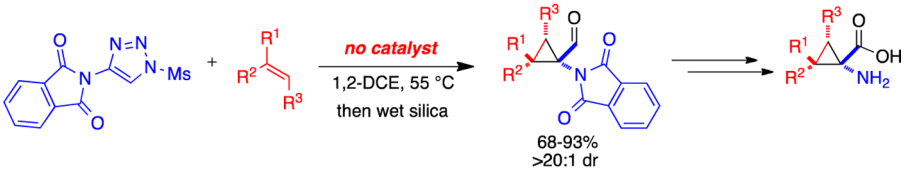
ABSTRACT



Warming of 4-phthalimido-*N*-mesyl-1,2,3-triazole in the presence of alkenes followed by silica gel induced hydrolysis results in a highly diastereoselective and catalyst-free entry to *N*-phthalimidocyclopropanecarboxaldehydes.

Cyclopropane α-amino acids have attracted much attention over the years due to their significant biological properties.[1] They are constituents of agrochemicals[2] and therapeutic agents[3] and have been applied to the design of conformationally restricted peptides.[4] Several approaches have been developed for the synthesis of cyclopropane α-amino acids.[1] One of the most established approaches has been the metal-catalyzed reaction of diazo compounds with alkenes, which proceed via carbenoid intermediates.[5] We have demonstrated that donor/acceptor carbenoids routinely undergo highly diastereoselective cyclopropanation reactions.[6] When the reaction is conducted with styryldiazoacetates in the presence of Rh_2(*S*-DOSP)$_4$ as a chiral catalyst, the cyclopropanations are highly diastereoselective and enantioselective. The resulting products can be converted to cyclopropane α-amino acids, but this requires a four-step process.[5a] Alternative strategies using acceptor/acceptor carbenoids have been developed since

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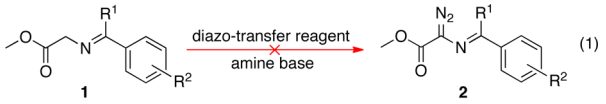
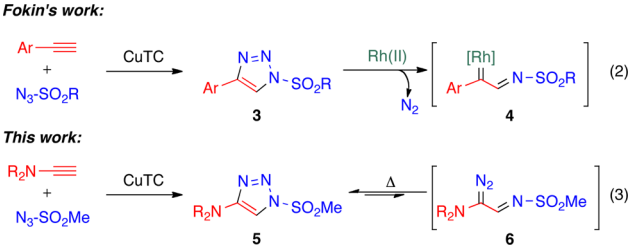
then. They involve either potential hazardous α-nitrodiazo compounds[5f,g] or dicarbonyl derivatives[5e] which require subsequent Curtius-type rearrangement of one of the carbonyl groups or suffer from low diastereoselectivity. In this paper, we describe a direct approach for the diastereoselective synthesis of cyclopropane α-amino acids using donor/acceptor carbenes in which the donor group is a protected amine functionality.

Donor/acceptor carbenoids have become widely used in organic synthesis.[6] Currently, the donor group is limited to aryl, heteroaryl, vinyl, alkynyl, or chloro.[7] These groups stabilize not only the electron-deficient carbenoid by electron donation through resonance but also the diazo compound by being inductively electron accepting.[8] Considering the importance of donor/acceptor carbenoids, expanding the nature of the donor group would be highly beneficial. All of our attempts to prepare diazo compounds with a protected amine donor group have been unsuccessful. Representative examples of some of our unsuccessful efforts can be seen in eq 1. The rapid evolution of dinitrogen during their attempted synthesis suggests that the diazo compounds **2** were decomposing as they were being formed. From these studies, we concluded amino-substituted diazo compounds would be best prepared *in situ*; however, the diazo transfer reaction is unlikely to be useful in this type of scenario due to the incompatibility of the transfer agent, amine base, and solvent with the subsequent metal-catalyzed reaction.[9]



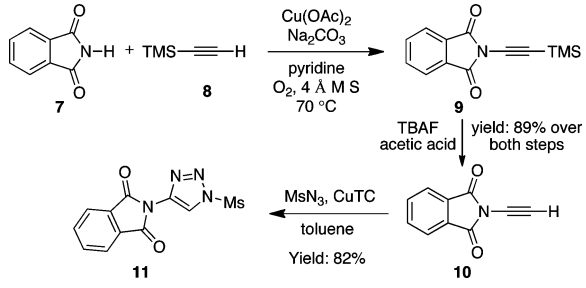
R^1 = H, Me, OMe, Ph, CF_3; R^2 = EDG and EWG

A potential solution to the *in situ* generation of α-amino-substituted carbenoids comes from the recent studies by Fokin,[10] which showed that *N*-sulfonyl-4-aryl-1,2,3-triazoles could be used as precursors to donor/acceptor carbenoids in the presence of a dirhodium(II) catalyst (eq 2). The resulting *aza*-vinyl carbenoids underwent not only a few classic donor/acceptor reactions including enantioselective cyclopropanation of olefins[10a,b] and C−H insertion reactions of alkanes[10c] but also a few unusual transformations such as transannulation reactions with nitriles[10d] and asymmetric intramolecular deoxygenation of sulfones.[10e] These studies have focused on the generation of rhodium(II)-stabilized α-aryldiazo sulfonylimines. Extension of this approach to *N*-sulfonyl-4-amino-1,2,3-triazoles would lead to the formation of α-amino substituted carbenoid intermediates (eq 3).



We envisioned that a 4-*N*-phthalimido-*N*-sulfonyl-1,2,3-triazole **11** would be a suitable precursor to an amino-functionalized donor/acceptor carbenoid (Scheme 2). A reasonable synthetic approach to **11** would be the copper(I)-catalyzed azide−alkyne cycloaddition.[11] The synthetic approaches to ynimides is relatively limited.[12] A recent report of an experimentally simple copper-catalyzed aerobic oxidative amidation of terminal alkynes resulting in the efficient synthesis of ynamides appeared ideal for our needs.[13] Adaptation of this procedure to phthalimide **7** and TMS-acetylene **8** in the presence of 20 mol % of $Cu(OAc)_2$ generated the TMS-protected ynimide **9**, which was then deprotected to furnish the *N*-ethynylphthalimide **10** in 89% yield over both steps (Scheme 1). The ynimide **10** was then transformed into the benchtop stable 4-phthalimido-*N*-mesyl-1,2,3-triazole **11** through a copper-catalyzed alkyne−azide cycloaddition by treatment with mesyl azide in the presence of copper(I) thiophene-2-carboxylate (CuTC).[11]

Scheme 1. Synthesis of 4-*N*-Phthalimido-*N*-sulfonyl-1,2,3-triazole



The metal-catalyzed reaction of the triazole **11** in the presence of styrene was examined as a test reaction. To our delight, **11** reacted smoothly at 55 °C in the presence of

(7) (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2009**, *110*, 704–724. (b) Denton, J. R.; Cheng, K.; Davies, H. M. L. *Chem. Commun.* **2008**, 1238. (c) Denton, J. R.; Davies, H. M. L. *Org. Lett.* **2009**, *11*, 787–790. (d) Hansen, J.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009**, *74*, 6555–6563. (e) Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 17211–17215. (f) Davies, H. M. L.; Nikolai, J. *Org. Biomol. Chem.* **2005**, *3*, 4176–4187.

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(9) For an example of a donor/acceptor carbene containing an α-amino group derived from an oxirene, see: Li, H.; Antoline, J.; Yang, J.; Al-Rashid, Z.; Hsung, R. *New J. Chem.* **2010**, *34*, 1309–1316.

(10) (a) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034–18035. (b) Grimster, N.; Zhang, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2010**, *132*, 2510–2511. (c) Chuprakov, S.; Malik, J. A.; Zibinsky, M.; Fokin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 10352–10355. (d) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972–14974. (e) Selander, N.; Fokin, V. V. *J. Am. Chem. Soc.* **2012**, *134*, 2477–2480.

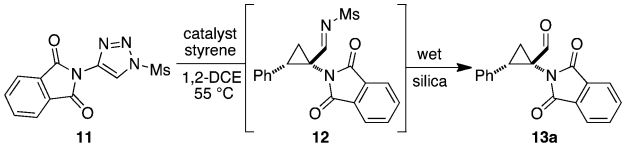
(11) (a) Raushel, J.; Fokin, V. V. *Org. Lett.* **2010**, *12*, 4952–4955. (b) Zibinsky, M.; Fokin, V. V. *Org. Lett.* **2011**, *13*, 4870–4872. (c) Raushel, J.; Pitram, S. M.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3385–3388. Mesyl azide was used for better atom economy; other sulfonyl azides such as tosyl azide can be used. Fokin (ref 9) has also shown this to be the best sulfonyl azide for the generation of rhodium(II)-stablized carbenoids. Caution should be taken when using this reagent.

(12) Sueda, T.; Oshima, A.; Teno, N. *Org. Lett.* **2011**, *13*, 3996–3999.

(13) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833–835.

either Rh_2(*S*-DOSP)$_4$ or Rh_2(*S*-PTAD)$_4$ to provide cyclopropane imine **12** (Table 1). Hydrolysis of **12** was achieved by simply adding wet silica to the reaction flask to furnish the aldehyde **13a** in excellent yield (92−93%) and high diastereoselectivity (>20:1). Even though Rh_2(*S*-DOSP)$_4$ or Rh_2(*S*-PTAD)$_4$ are exceptional chiral catalysts for donor/acceptor carbenoids,[6] **13** was formed as a racemate. A control experiment without a rhodium catalyst revealed that **13a** is still formed in high yield (89%) and diastereoselectivity (>20:1). Therefore, the formation of **13a** is unlikely to be a rhodium-catalyzed process even though the reaction is highly diastereoselective. Earlier studies have shown that the metal-free thermal cyclopropanation with aryldiazoacetates can also be highly diastereoselective.[14]

Table 1. Representative Reaction Screen[a]

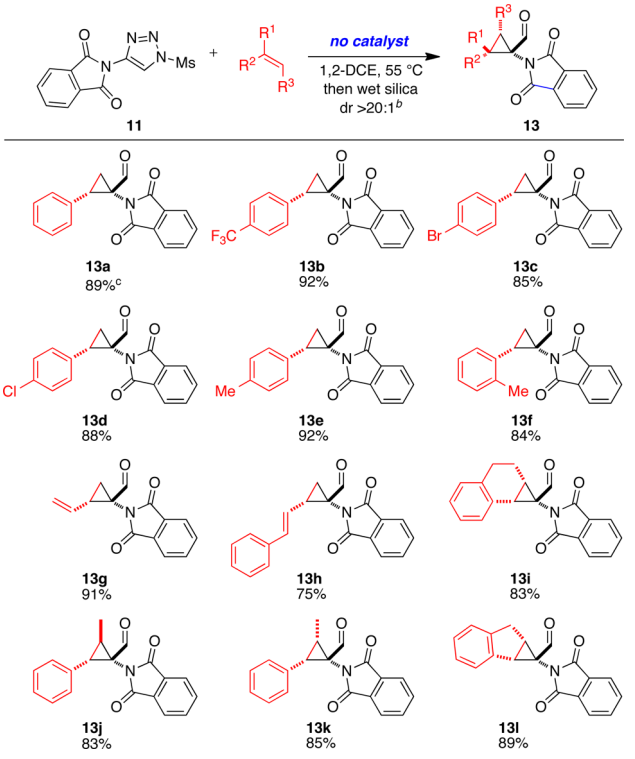


entry	catalyst	temp (°C)	% yield **13a**[b]	dr[c]	% ee
1	Rh_2(S-PTAD)$_4$	55	93	>20:1	<2
2	Rh_2(S-DOSP)$_4$	55	92	>20:1	<2
3	none	55	89	>20:1	–

[a] Conditions: triazole **11** (0.26 mmol), styrene (1.28 mmol), Rh(II) catalyst (0.0026 mmol), 1,2-DCE (2 mL), 12 h. [b] Isolated yield; See Supporting Information for more details. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Having discovered that the cyclopropanation was not metal catalyzed, the scope of the catalyst-free, thermal reaction was examined (Scheme 2). A broad range of terminal and internal alkenes were transformed into the corresponding cyclopropanecarboxaldehydes **13a**−**13l** in good to excellent yields (75−92%) with excellent diastereoselectivity (>20:1). Styrenes possessing either an electron-rich or -deficient aryl group reacted smoothly to produce cyclopropanes **13a**−**f**. 1,3-Butadiene and 1-phenyl-1,3-butadiene readily gave monocyclopropanecarboxaldehydes **13g** and **13h**, respectively. The influence of the alkene geometry is not as profound in the thermal reactions as compared to dirhodium-catalyzed reactions,[15] as both *trans*-*β*-methylstyrene and *cis*-*β*-methylstyrene were readily transformed into the corresponding cyclopropanecarboxaldehydes **13j** and **13k**, respectively. Cyclic substrates also furnished cyclopropanes **13i** and **13l** in excellent yield and diastereoselectivity. It is important to note that unlike typical rhodium-catalyzed reactions,[5] there is no need to add the carbenoid precursor slowly because there is unlikely to be a buildup of diazo compounds using the triazole starting materials (eq 3).

Scheme 2. Scope with Respect to Olefin[a]



[a] Conditions: triazole **11** (0.26 mmol), styrene (1.28 mmol), 1,2-DCE (2 mL), 12 h, then hydrolysis with wet silica. Reported yields are isolated. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield: 86% with 1.5 equiv of styrene.

The synthesis of the α-amino cyclopropanecarboxaldehydes starting from *N*-ethynylphthalimide **10** can be conducted in a one-pot, two-step synthesis as illustrated in Table 3. *N*-Ethynylphthalimide **10** was treated with mesyl azide (1.1 equiv) in the presence of CuTC (10 mol %) in chloroform to generate the intermediate 4-phthalimido-*N*-mesyl-1,2,3-triazole **11**. After 12 h, the styrene derivative (1.5 equiv) was added to the reaction mixture and the reaction media were warmed to 55 °C for 12 h. Once the allotted time had passed, wet silica gel was added to the reaction to furnish the cyclopropanecarboxaldehydes **13a**−**f** in good yields (74−85%) with excellent diastereoselectivity (>20:1). The yields of the one-pot, two-step reaction (Table 2) are comparable to the yields presented in Scheme 2. Key features to this one-pot reaction are the requirement of only a slight excess of the olefin and the formation of only dinitrogen and methanesulfonamide as byproducts.

The initial product of the thermal cyclopropanation, the sulfonyl imines, is a synthetically versatile intermediate. This is illustrated with examples of *in situ* manipulations of the sulfonyl imine **12** (Scheme 3). Reduction of **12** with sodium borohydride provided easy access to the sulfonated

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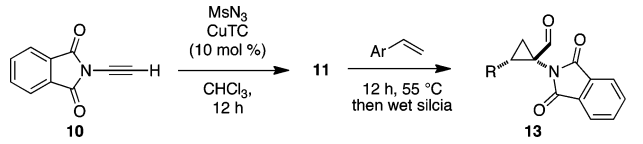
(15) Thompson, J. L.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090–6091.

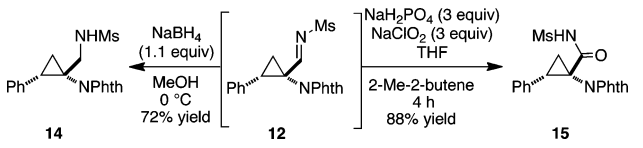
Table 2. Development of a One-Pot, Two-Step Reaction[a]



entry	Ar	product	% yield[b]	dr[c]
1	Ph	**13a**	85	>20:1
2	4-CF_3Ph	**13b**	77	>20:1
3	4-BrPh	**13c**	74	>20:1
4	4-ClPh	**13d**	80	>20:1
5	4-MePh	**13e**	79	>20:1
6	2-MePh	**13f**	82	>20:1

[a] Conditions: **10** (0.58 mmol), mesyl azide (0.64 mmol), CuTC (0.058 mmol), 4 Å MS, and $CHCl_3$ (3 mL) were stirred for 12 h at rt, then styrene (0.88 mmol) was added, and the reaction was stirred for 12 h at 55 °C. Hydrolysis of **11** with wet silica added to the reaction mixture. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude reaction.

Scheme 3. Representative Synthetic Variation from the Imine



monoamine **14** in good yield.[10c] The addition of sodium chlorite under Pinnick oxidation conditions gave the corresponding sulfonyl amide **15** in high yield.[16]

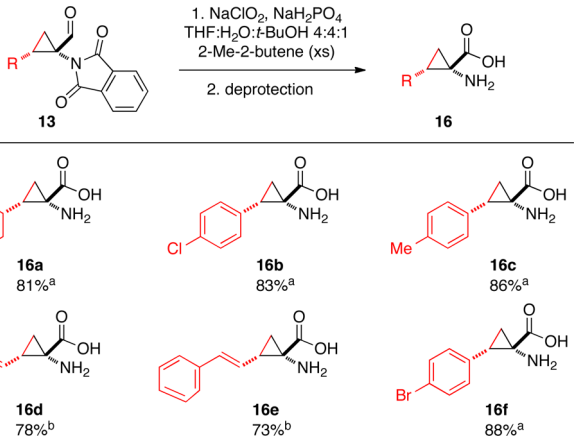
The most attractive feature of this thermal cyclopropanation is the opportunity for ready access of cyclopropane α-amino acids as illustrated in Scheme 4. The *N*-cyclopropanecarbaldehyde phthalimide derivatives **13** were converted to the free α-amino acid by first conducting a mild Pinnick oxidation of the aldehyde to provide the corresponding acids. Then the *N*-phthaloyl acid was deprotected by either direct acid hydrolysis or a modified sodium borohydride reduction[17] of the phthaloyl group to give the α-amino acid derivatives **16a**–**f** in 73–88% yields over both steps.

There are two plausible mechanisms possible for this thermal cyclopropanation. The first would be the classic 1,3-dipolar cycloaddition to form a pyrazoline intermediately followed by a thermal dinitrogen extrusion event to form the cyclopropane.[5c] The second would be a thermal decomposition of the diazo compound, which would then

(16) Mohamed, M. A.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2009**, *50*, 3436–3438.

(17) Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093–2096.

Scheme 4. Unmasking of the Cyclopropyl α-Amino Acid



[a] Deprotection A: reflux in acetic acid with 3 M HCl for 4 h. [b] Deprotection B: $NaBH_4$ (6 equiv) in 6:1:0.5 *i*PrOH/H_2O/aq $NaHCO_3$ for 8 h and then dry HCl in ether.

undergo a direct cyclopropanation. Although it is not possible to distinguish unequivocally between the two mechanisms at this time, the carbene mechanism is more consistent with the observed results. The initial results directed toward the synthesis of α-amino diazo compounds revealed such compounds were very prone to thermal decomposition. The inability to influence the reaction with the highly active dirhodium catalysts suggests that the diazo compounds are very short-lived species. Unless the 1,3-dipolar cycloaddition is extremely facile with α-amino diazo compounds, then the intermediacy of the amino-stabilized carbene is the more likely scenario.

In conclusion, 4-phthalimido-*N*-mesyl-1,2,3-triazole undergoes a facile thermal reaction to generate a donor/acceptor carbene, in which the donor group is the phthalimido group. This carbene undergoes highly diastereoselective cyclopropanation with a range of alkenes and dienes, leading to a ready access to cyclopropane α-amino acids in an experimentally simple way. Current studies are directed toward a better understanding of the thermal dinitrogenation mechanism, developing an enantioselective metal-catalyzed reaction of aminotriazoles and expanding the scope of the chemistry to other classes of substituted triazoles.

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Supporting Information Available. Full experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.