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α-Diazo-β-ketonitriles: Uniquely Reactive Substrates for Arene and Alkene Cyclopropanation

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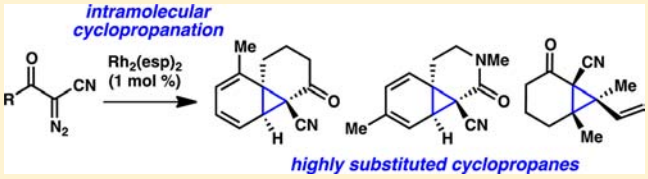
Supporting Information

ABSTRACT: An investigation of the intramolecular cyclopropanation reactions of α-diazo-β-ketonitriles is reported. These studies reveal that α-diazo-β-ketonitriles exhibit unique reactivity in their ability to undergo arene cyclopropanation reactions; other similar acceptor−acceptor-substituted diazo substrates instead produce mixtures of C−H insertion and dimerization products. α-Diazo-β-ketonitriles also undergo highly efficient intramolecular cyclopropanation of tri- and tetrasubstituted alkenes. In addition, the α-cyano-α-ketocyclopropane products are demonstrated to serve as substrates for S_N2, S_N2', and aldehyde cycloaddition reactions.



INTRODUCTION

Transition-metal-catalyzed cycloaddition reactions between diazo compounds and alkenes or arenes are widely employed for the preparation of cyclopropanes,[1] versatile synthetic intermediates that can be elaborated to cyclopropane-containing natural products or pharmaceuticals.[2] In addition, the ∼28 kcal/mol of ring strain associated with the three-membered ring endows these compounds with the ability to participate in a variety of transformations that proceed by C−C bond scission. These reactions include sigmatropic processes such as vinyl-cyclopropane rearrangements[3] and rate-accelerated Cope and retro-Claisen rearrangements,[4] nucleophilic displacement reactions,[5] and a variety of cycloaddition reactions.[6] As a result of their synthetic utility, the development of new catalytic cyclopropanation reactions has been the subject of intense study by a number of prominent researchers.[1,7,8] Despite remarkable advances in the state-of-the-art over the past several decades, certain cyclopropane substitution patterns nonetheless remain challenging to access by metal-catalyzed diazo cycloaddition chemistry. In particular, efforts to prepare highly substituted cyclopropanes by the cycloaddition between disubstituted diazo groups and either arenes, tri-, or tetrasubstituted olefins are often complicated by competing C−H insertion processes, resulting in poor yields of the desired product.[9] Thus, in order to gain access to the full complement of cyclopropane structural patterns, continued efforts to expand the scope of cyclopropanation reactions are required.

Our own foray into the area of cyclopropanation research grew out of a total synthesis program focused on the preparation of the natural product salvileucalin B (**1**).[10] Salvileucalin B is an unusual diterpenoid that contains a stable norcaradiene embedded within its carbocyclic framework. Retrosynthetically, we envisioned constructing the norcaradiene of **1** by an intramolecular Buchner-type reaction[11,12] of an appropriately functionalized α-diazo-carbonyl compound (**3**, Figure 1).[13,14] To enable elaboration of norcaradiene **2** to **1**, it

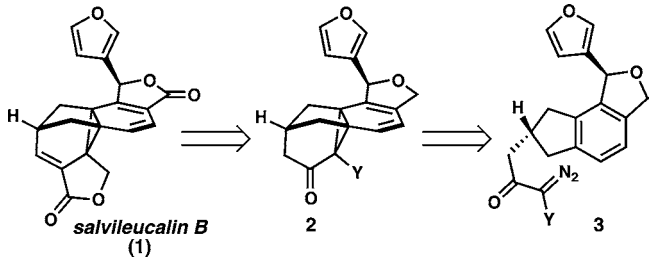


Figure 1. Retrosynthetic analysis of salvileucalin B.

was deemed critical to utilize a disubstituted diazo substrate that possessed a functional handle for installation of the γ-lactone (e.g., **3**, Y ≠ H).

However, a survey of the literature describing *intra*molecular Buchner-type reactions of diazo compounds revealed that subtle changes in the substrate can dramatically affect the yields of the norcaradiene products.[15] For example, in systems bearing three atoms between the arene and diazo group (Figure 2, **4**, n = 1), cyclopropanation is typically favored, since C−H insertion would produce a four-membered ring.[15b,d] On the other hand, C−H insertion processes become competitive in substrates containing four-atom linkers (**4**, n = 2), since five-membered ring formation is facile.[15b,16] The diazo substitution also critically influences the ratio of arene cyclopropanation to C−H insertion. Whereas terminal α-diazoketones (**4**, Y = H) are excellent substrates for arene cyclopropanation, the corresponding α-diazo-β-ketoesters (**4**, Y = CO_2R) strongly favor C−H insertion or carbene dimerization.[10b,15b,17] Finally, the metal

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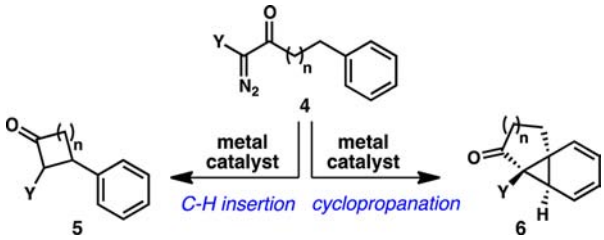
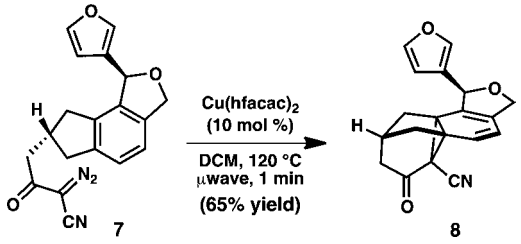


Figure 2. Divergent reactivity: cyclopropanation vs C−H insertion.

catalyst and ligand framework also significantly influence the ratio of cyclopropanation to C−H insertion.[15a,b]

Consistent with the reactivity trends described above, there were no prior examples of intramolecular Buchner reactions to generate fully substituted cyclopropanes at the outset of our research. Moreover, there were no examples of intramolecular Buchner reactions using acceptor−acceptor (A−A) substituted diazo substrates possessing a four-atom linker, such as the α-diazo-β-ketoester (**3**, Y = CO_2Me) we envisioned utilizing in the synthesis of salvileucalin B.[18] After extensive experimentation, we found that the α-diazo-β-ketonitrile moiety was unique among A−A substituted diazo substrates in its ability to undergo arene cyclopropanation, a discovery that led to the successful synthesis of **1** via the Cu-catalyzed cyclopropanation of **7** (Scheme 1).[10a,b,19] Inspired by this novel reactivity and

Scheme 1. Cu-Catalyzed Arene Cyclopropanation of 7



mindful of an apparent gap in the existing technology, we recognized that this transformation could potentially be of broad utility well beyond our synthetic studies toward salvileucalin B. Thus, we initiated a program aimed at investigating the cyclopropanation reactions of α-diazo-β-ketonitriles, the results of which are described herein.

RESULTS AND DISCUSSION

Our initial efforts focused on studying the reactivity of simple arylhexanone systems toward Buchner-type cyclopropanation. The α-diazo-β-ketonitriles (**12**) were easily prepared in three steps from aryl bromides **9** by Negishi cross coupling with organozinc **10**,[20] homologation to the ketonitrile,[10b] and diazo transfer[21] (Scheme 2). This sequence allows facile access to a variety of arene substitution patterns from a range of commercially available aryl bromide starting materials.

Using the parent phenyl substrate **12a**, a screen of metal complexes revealed that while $Cu(hfacac)_2$ provided norcaradiene **13a** in 54% yield, several dirhodium tetracarboxylate salts proved more effective (Table 1, entries 2, 7−9, and 11). Of the Rh^{II} catalysts investigated, the more electron-deficient catalysts provided higher yields of **13a** (entries 7−9). This trend is consistent with that reported by Padwa and co-workers, whose studies on the Buchner reactions of terminal diazo ketones determined that $Rh_2(pfb)_4$ favors cyclopropanation,

Scheme 2. Substrate Preparation

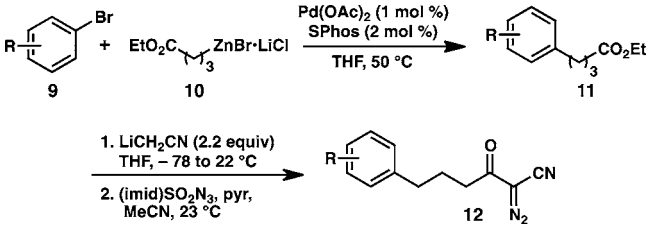
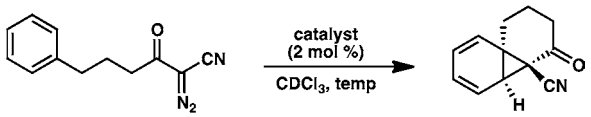


Table 1. Catalyst Screen



entry	catalyst	temp (°C)	yield (%)[a]
1	$Cu(hfacac)_2$	90	24
2	$Cu(hfacac)_2$[b]	90	54
3	$Cu(acac)_2$	120	4
4	Co(salen)	22	0
5	Co(salen)	120	0
6	$[Ir(cod)Cl]_2$	120	0
7	$Rh_2(pfb)_4$	22	65 (70)[c]
8	$Rh_2(tfa)_4$	22	54
9	$Rh_2(OAc)_4$	22	60 (65)[c]
10	$Rh_2(cap)_4$	22	2
11	$Rh_2(esp)_2$	22	58 (70)[c]

[a]Yield determined by ^1H NMR analysis versus an internal standard. [b]5 mol % catalyst was employed. [c]Isolated yield; substrate is added by syringe pump.

while $Rh_2(cap)_4$ favors C−H insertion.[15b] The commercially available bridging carboxylate-containing catalyst $Rh_2(esp)_2$ developed by Du Bois[22] also cleanly provided **13a**. Taken together, these findings stand in contrast to our studies on the cyclopropanation of tetrasubstituted arene **7** (Scheme 1), which determined that $Cu(hfacac)_2$ was optimal while Rh^{II} catalysts performed poorly.[10b] We attribute this dichotomy in reactivity to the sensitivity of Rh^{II} catalysts to the steric profile of the substrate. Compound **7** is a particularly challenging substrate, since the geometric constraints require cyclopropanation at the equivalent of a tetrasubsituted alkene, with the additional steric encumbrance of an *ortho*-substituent. Thus, the Rh-carbenoid derived from **7** encounters increased steric hindrance in the cyclopropation transition state, which destabilizes this pathway relative to the more sterically accessible C−H insertion pathways. On the other hand, our findings, as well as those of Mander and co-workers,[15a] suggest that Cu-carbenoids are less sensitive to substrate sterics and typically provide higher chemoselectivity for cyclopropanation over C−H insertion.[23] However, the Cu-catalyzed reactions also require higher temperatures to initiate dediazotization; the harsher reaction conditions can result in lower overall yields and the need for higher catalyst loadings, despite the often-improved chemoselectivity. Ultimately, these studies determined that for simple, sterically unencumbered arenes such as **12a**, the best yields are obtained by slow addition of α-diazo-β-ketonitrile **12a** to a solution of either $Rh_2(esp)_2$ or $Rh_2(pfb)_4$ as the catalyst (entries 7 and 11). All subsequent studies were conducted using the slow addition protocol (see Supporting Information for details) and one of these two catalysts, as indicated.

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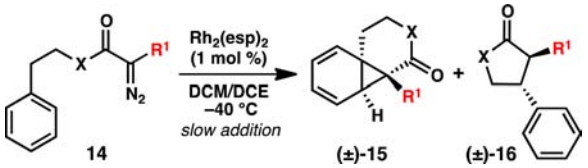
Our studies toward salvileucalin B revealed a profound effect by the diazo substitution on the product distribution of the reaction.[10b] To systematically study this effect, a series of A−A diazo substrates (**14**) was prepared (Table 2). Consistent with previous work in our group and by others, the terminal diazo compound (**14a**, R^1 = H) was found to cleanly undergo arene cyclopropanation, delivering norcaradiene **15a** in quantitative yield (entry 1). However, even the relatively minor perturbation of changing R^1 from proton to methyl drastically affected the chemoselectivity, with the reaction now favoring C−H insertion to give cyclopentanone **16b** (entry 2). The propensity of **14b** to undergo C−H insertion is in stark contrast to the corresponding 4-diazo-1-phenylpentan-3-one (**17**), a compound containing one fewer methylene in the linker, which when treated with catalytic $Rh_2(OAc)_4$ is reported to provide an equilibrating mixture of norcaradiene **18** and cycloheptatriene **19** in 67% yield (Scheme 3).[15d] This divergent reactivity clearly reflects the preference for five- over four-membered ring formation.

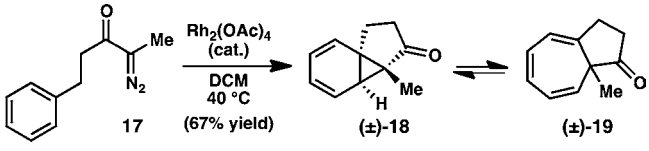
Table 2. Influence of Diazo Substitution on Chemoselectivity



entry	R^1	X	yield **15** (%)	yield **16** (%)
1	H (**14a**)	CH_2	>95	n.d.[a]
2	Me (**14b**)	CH_2	n.d.	43
3	COMe (**14c**)	CH_2	n.d.	32
4	CO_2Me (**14d**)	CH_2	n.d.	45
5	NO_2 (**14e**)	CH_2	n.d.	28
6	CN (**12a**)	CH_2	70 (**13a**)	n.d.
7	CO_2Me (**14f**)	NMe	n.d.	50

[a]n.d. = not detected.

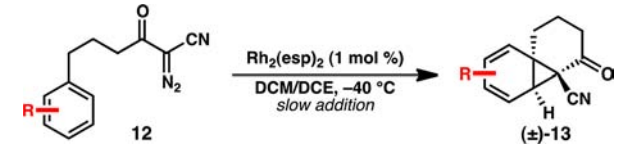
Scheme 3. Kennedy and Co-workers' Arene Cyclopropanation of 4-Diazo-1-phenylpentan-3-one[15e]



A further investigation of substrates revealed that, in general, disubstituted diazo compounds containing four-atom linkers favor C−H insertion over arene cyclopropanation (Table 2). Thus, treatment of a variety of A−A substituted substrates (R^1 = COMe, CO_2Me, NO_2) with catalytic $Rh_2(esp)_2$ provides modest yields of cyclopentanone **16**; in these cases, no norcaradiene is detected in the crude reaction mixture. The mass balance was determined by ^1H NMR and LC−MS to be a mixture of dimerization products. Of the disubstituted diazo substrates evaluated here, α-diazo-β-ketonitrile **12a** was *uniquely* effective in providing the norcaradiene product (**13a**).[24]

In addition to studying the effect of diazo substitution, the influence of arene substitution on the yield of cyclopropanation was also evaluated (Table 3). Substrates bearing electron-donating groups (EDGs) in the *ortho*, *meta*, or *para* positions react efficiently with low catalyst loadings. However, in the case of *m*-substituted substrates (entries 9, 10), the resulting norcaradienes readily undergo C−C bond scission and rearomatization to produce the benzo-fused cycloheptanone products **13i** and **13j**.[25] In contrast, norcaradienes with *p*- or *o*-EDGs (entries 2, 3, 12, and 13) are more stable and can be isolated when the reaction is quenched with pyridine (to attenuate the Lewis acidity of the residual rhodium) and chromatographically purified using Florisil.

Table 3. Scope of Norcaradiene Formation



Entry	Yield (%)[a]	Entry	Yield (%)[a]
1	70 70[b]	9	93
2	80	10	81
3	90	11	66
4	67	12	81
5	63 72[b]	13	47
6	36 64[b]	14	<5 24[b]
7	20 50[b]		
8	31 40[b]	15	50 58[b]

[a]Isolated yield. [b]Conducted at 0 °C using $Rh_2(pfb)_4$ (1 mol %) as catalyst.

Substrates bearing electron-withdrawing groups (EWGs) also undergo arene cyclopropanation to provide stable norcaradienes; however, these systems are less reactive, and the products are typically generated in lower yields using $Rh_2(esp)_2$ under the standard reaction conditions (entries 5−7). Notably, for these substrates, use of the more reactive $Rh_2(pfb)_4$ catalyst provided better yields of the norcaradiene products.[26] The use of $Rh_2(pfb)_4$ also delivered higher yields of the norcaradienes

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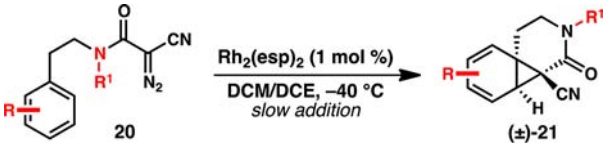
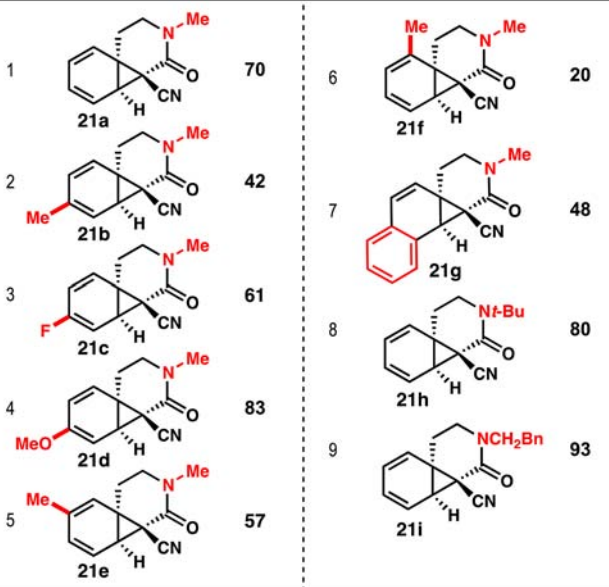
from more sterically encumbered substrates (entries 8, 14, 15). Only when using $Rh_2(pfb)_4$ with these more hindered α-diazo-β-ketonitrile systems do we observe detectable quantities of C−H insertion products (~5−10%). For unsymmetrical substrates (9−13, 15), the arene cyclopropanation reaction occurs regioselectively at the less hindered site.[15d] The exception is naphthyl substrate **12h**, which provides a modest yield of tetracycle **13h** because of competitive formation of the positional isomer and dimerization product. The electronic nature of the *m*- or *o*-substituent does not exert a significant effect with regard to regioselectivity (see entries 9−13).

A series of the analogous α-diazo-β-cyanoamides were also prepared and studied (Table 4). For these substrates, the

Table 4. Buchner Reaction of α-Diazo-β-cyanoamides



Entry	Yield (%)[a]	Entry	Yield (%)[a]
1	70	6	20
2	42	7	48
3	61	8	80
4	83	9	93
5	57		



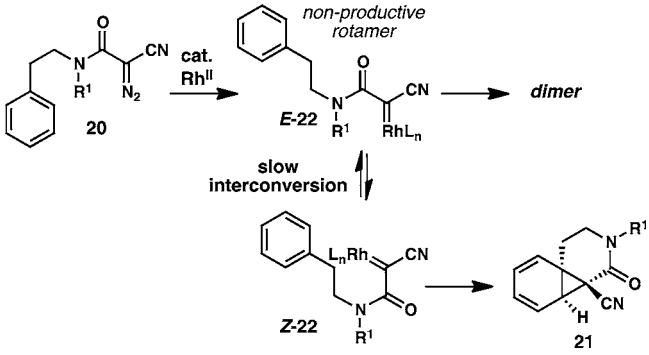
[a]Isolated yield.

norcaradiene products are stable and isolable regardless of the substitution pattern or purification method. Similar reactivity trends to those for the α-diazo-β-ketonitriles were observed; however, the yields of norcaradienes were typically lower because of increased formation of carbene dimerization products.

It has been proposed that metal-carbenoids generated from amide-linked diazo substrates (**20**) exist as two slowly interconverting rotamers, (*Z*)-**22** and (*E*)-**22** (Scheme 4).[17,27] Only (*Z*)-**22** is geometrically capable of arene cyclopropanation; if rotation around the amide bond is slow relative to the rate of the competing dimerization process, then the population of (*E*)-**22** could contribute to increased dimer formation while lowering the overall yield of norcaradiene **21**.

Two substrates were designed to probe this hypothesis. *N*-Substitution with a *tert*-butyl group (**20h**) was expected increase the population of the productive rotamer (*Z*)-**22** (R^1 = *t*-Bu) and thereby increase the yield of norcaradiene.

Scheme 4. Effects of Amide Rotamers on Arene Cyclopropanation



Consistent with this hypothesis, norcaradiene **21h** was isolated in 80% yield (Table 4, entry 8), an improvement relative to the 70% yield obtained for **21a**. Moreover, the symmetric diphenethyl substrate **20i**, in which the amide conformers are identical, provides norcaradiene **21i** in excellent yield (entry 9).

Given the unique reactivity of α-diazo-β-ketonitriles for arene cyclopropanation, we sought to explore the analogous reactions of highly substituted alkenes. Although the transition-metal-catalyzed cyclopropanation of alkenes has been extensively studied, the *intramolecular* cyclopropanation of tri- and tetrasubstituted olefins with A−A substituted carbenoids remains underdeveloped. To our knowledge, there are very few examples of intramolecular metal-catalyzed cyclopropanation reactions of tri- and tetrasubstituted alkenes using A−A diazo substrates.[9a,b]

We were therefore pleased to find that the intramolecular cycloaddition of alkenyl α-diazo-β-ketonitriles proceeds smoothly under mild conditions (Table 5). In the case of tetrasubstituted alkene substrates **23b** and **23e−g**, the corresponding cyclopropane products contain three vicinal all-carbon quaternary centers and are formed in good yields as single diastereomers.

Notably, the alkene cyclopropanation reactions are much less sensitive to water or parameters such as concentration, substrate addition rate, and temperature than those of the corresponding aryl systems. Of all the alkenyl substrates tested in this report, only the unsaturated ester **23h** (R^1 = H, R^2 = CO_2t-Bu, R^3 = Me) failed to provide the desired cyclopropane, affording instead the C−H insertion product **25** (entry 8).[28] To our knowledge, these are the first examples of tetrasubstituted alkenes undergoing intramolecular cyclopropanation with A−A substituted carbenoids, and we anticipate that these diastereoselective reactions to prepare bi- and tricyclic compounds will find application in a variety of synthetic contexts.

The unique propensity of α-diazo-β-ketonitriles toward arene and alkene cyclopropanation warrants some discussion. One significant difference between Rh-carbenoids derived from α-diazo-β-ketonitriles and other A−A substituted diazo compounds is the linear geometry of nitrile. For example, ester and ketone substituted carbenoids are proposed to adopt out-of-plane conformations in which the π-system of the carbonyl and the vacant 2p orbital of the carbenoid are orthogonal, preventing delocalization (Figure 3, b).[23a,29] Alternatively, the nitrile is intrinsically coplanar with the Rh-carbenoid; this conformational effect likely enhances the electrophilicity of the carbenoid (Figure 3, a). That more electrophilic carbenoids favor cyclopropanation over C−H insertion is consistent with

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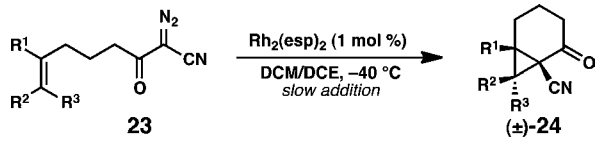
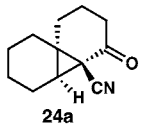
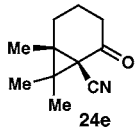
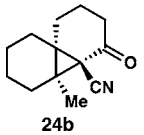
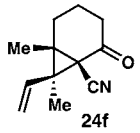
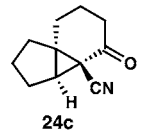
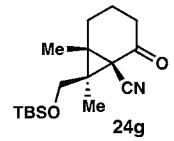
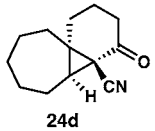
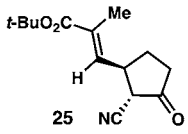
Table 5. Cyclopropanation of Various Alkenes



Entry		Yield (%)[a]	Entry		Yield (%)[a]
1	 24a	82	5	 24e	90
2	 24b	76	6	 24f	79
3	 24c	93	7	 24g	93
4	 24d	92	8	 25	40

[a]Isolated yield.

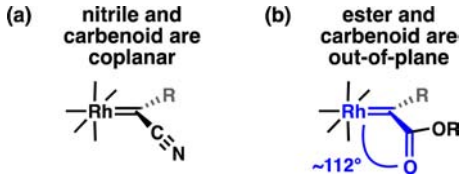
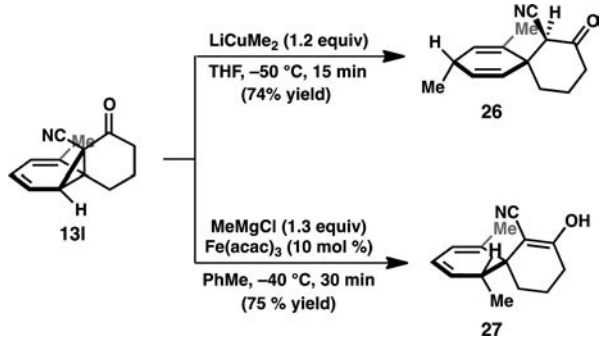


Figure 3. Conformational considerations of acceptor-substituted carbenoids.

Padwa's reports on the ligand effects of dirhodium catalysts, which demonstrated that more electron deficient Rh complexes improve the ratio of cyclopropanation to C–H insertion.[15b] Moreover, the relatively small steric profile of the nitrile likely minimizes destabilizing nonbonding interactions between the Rh-carbenoid and the arene/alkene in the cyclopropanation transition structure, while the out-of-plane conformations of esters or ketones sterically obstruct the approach of the arene/alkene to the carbenoid. These effects were recently proposed by Charette and co-workers to impart unique reactivity to cyano-substituted carbenoids for asymmetric *intermolecular* cyclopropanation reactions.[30] Similarly, Fox and co-workers propose that 5- and 6-membered *cyclic* Rh-carbenoids are constrained such that the carbonyl is coplanar with the carbenoid, which minimizes steric interactions during intermolecular cyclopropanation reactions and allows these processes to out-compete β-hydride migration.[7a]

The remarkable reactivity of α-diazo-β-ketonitriles enables the preparation of highly substituted cyclopropanes with unprecedented chemical architectures, and we anticipated that these compounds could participate in a variety of ring-opening reactions. For example, A–A substituted vinyl cyclopropanes are known to undergo S_N2 and S_N2'-type ring-opening reactions.[5] We were therefore pleased to find that treatment of norcaradiene **13l** with lithium dimethylcuprate in THF results in S_N2' addition to provide spirofused bicyclic diene **26**, which is isolated as a single diastereomer (Scheme 5).[5d,31]

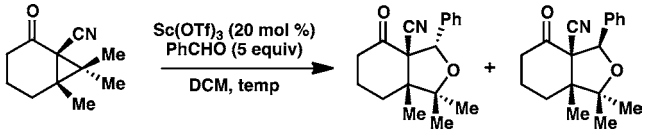
Scheme 5. Nucleophilic Ring-Opening of Norcaradiene 13l



Alternatively, **13l** undergoes clean S_N2 addition when treated with methylmagnesium chloride in the presence of catalytic $Fe(acac)_3$ to deliver the isomeric compound **27** as a single diastereomer.[5a,32] These transformations provide access to spirofused bicycles with complementary substitution patterns, and also highlight the utility of 7-cyano-7-keto-norcaradienes as substrates for stereocontrolled C–C bond formation.

There is also extensive literature describing the transformations of *donor*–acceptor (D–A) cyclopropanes.[6] For example, D–A cyclopropanes are useful synthons to access 2,5-disubstituted tetrahydrofurans via Lewis acid-mediated aldehyde cycloaddition reactions.[6d,e,33] Although cyclopropanes such as **24e** lack traditional donor groups (such as an arene, alkoxy, or amino substituent), we hypothesized that stabilization of the developing tertiary carbocation would enable cycloaddition.[34] We were pleased to find that treatment of **24e** with catalytic $Sc(OTf)_3$ and excess benzaldehyde provides tetrahydrofuran **28** in excellent yield, albeit as as a mixture of *endo*- and *exo*-diastereomers (Table 6). Interestingly, the

Table 6. Cycloaddition of "Donor"–Acceptor Cyclopropane 24e with Benzaldehyde



entry	temp (°C)	combined yield (%)	*endo*-28: *exo*-28	yield major (%)[a]
1	–20	80	3.4:1	61
2	40	85	1:3.3	65

[a]Isolated yield.

diastereoselectivity of the reaction was heavily dependent on the reaction temperature. At low temperatures, *endo*-diastereomer **28** is favored and can be isolated in 61% yield. Alternatively, when the reaction is conducted in refluxing dichloromethane, the thermodynamically more stable *exo*-product predominates (65% isolated yield).

Indeed, control experiments revealed that re-exposure of ***endo*-28** to the reaction conditions results in equilibration to the same 3.3:1 *exo*/*endo* ratio as observed at 40 °C. Although

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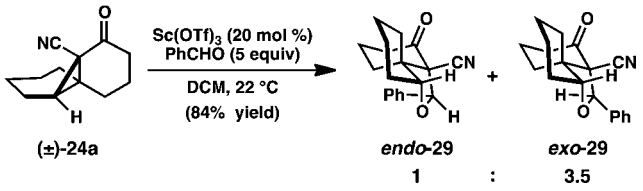
aldehyde cycloaddition reactions of D−A cyclopropanes have been extensively studied by Johnson, examples of this transformation without a true donor component (e.g., phenyl, vinyl, alkoxy, etc.) are less common.[33b,34] Similarly, we discovered that cyclopropane **24a**, bearing a secondary alkyl group as the "donor", also cleanly reacts with benzaldehyde under standard conditions to give a mixture of diastereomeric tricycles in good yield (Scheme 6). These studies clearly demonstrate the utility of α-cyano-α-ketocyclopropanes in aldehyde cycloaddition reactions for preparing polycyclic tetrahydrofuran derivatives.[35]

Scheme 6. Cycloaddition of "Donor"−Acceptor Cyclopropane 24a with Benzaldehyde



CONCLUSIONS

In conclusion, the intramolecular cyclopropanation of α-diazo-β-ketonitriles has been investigated. Of particular importance, α-diazo-β-ketonitriles are shown to demonstrate unique reactivity in their propensity to undergo arene cyclopropanation; other similar A−A substituted diazo substrates fail to deliver the Buchner-type product, favoring C−H insertion processes instead. In addition, α-diazo-β-ketonitriles undergo highly efficient intramolecular cyclopropanation of tri- and tetrasubstituted alkenes, which in the latter case provides access to products containing three contiguous all-carbon quaternary centers. These types of highly functionalized cyclopropane products with other A−A motifs are challenging to prepare by cycloaddition chemistry. We have also demonstrated that the α-cyano-α-ketocyclopropane products serve as excellent substrates for S_N2, S_N2', and aldehyde cycloaddition reactions. The development and application of enantio- and diastereoselective intramolecular cyclopropanation reactions of α-diazo-β-ketonitriles is the subject of ongoing research in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (c) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (d) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (e) Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75. (f) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.

(2) (a) Chen, D. Y. K.; Pouwer, R. H.; Richard, J. A. *Chem. Soc. Rev.* **2012**, *41*, 4631. (b) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (c) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (d) Salaun, J. *Chem. Rev.* **1989**, *89*, 1247. (e) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

(3) (a) Hudlicky, T.; Reed, J. W. *Angew. Chem., Int. Ed.* **2010**, *49*, 4864. (b) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197. (c) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229.

(4) (a) Sarpong, R.; Su, J. T.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 13624. (b) Boeckman, R. K.; Zhang, J.; Reeder, M. R. *Org. Lett.* **2002**, *4*, 3891. (c) Boeckman, R. K.; Reeder, M. R. *J. Org. Chem.* **1997**, *62*, 6456. (d) Hofmann, B.; Reissig, H. U. *Chem. Ber.* **1994**, *127*, 2327. (e) Boeckman, R. K.; Shair, M. D.; Vargas, J. R.; Stolz, L. A. *J. Org. Chem.* **1993**, *58*, 1295. (f) Hofmann, B.; Reissig, H. U. *Synlett* **1993**, *5*, 27. (g) Boeckman, R. K.; Flann, C. J.; Poss, K. M. *J. Am. Chem. Soc.* **1985**, *107*, 4359. See also: (h) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. In *Organic Reactions*; John Wiley & Sons, Inc.: New York, 2004.

(5) Selected examples: (a) Sherry, B. D.; Furstner, A. *Chem. Commun.* **2009**, *45*, 7116. (b) Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabo, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 8150. (c) Grieco, P. A.; Finkelhor, R. *J. Org. Chem.* **1973**, *38*, 2100. (d) Danishefsky, S.; Rovnyak, G.; Cavanaugh, R. *J. Chem. Soc., Chem. Commun.* **1969**, *12*, 636. See also: (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (f) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

(6) Seminal reports: (a) Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A.; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314. (b) Korotkov, V. S.; Larionov, O. V.; Hofmeister, A.; Magull, J.; de Meijere, A. *J. Org. Chem.* **2007**, *72*, 7504. (c) Sapeta, K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 8597. (d) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057. (e) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (f) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023. (g) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704. (h) Sugita, Y.; Kawai, K.; Yokoe, I. *Heterocycles* **2001**, *55*, 135. Reviews: (d) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (i) Reissig, H. U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.

(7) Selected carbenoid examples: (a) DeAngelis, A.; Dmitrenko, O.; Fox, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 11035. (b) Lu, H. J.; Dzik, W. I.; Xu, X.; Wojtas, L.; de Bruin, B.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 8518. (c) Xu, X.; Lu, H. J.; Ruppel, J. V.; Cui, X.; de Mesa, S. L.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 15292. (d) Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 19198. (e) Bull, J. A.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1895. (f) Zhu, S. F.; Xu, X.; Perman, J. A.; Zhang, X. P. *J. Am. Chem. Soc.* **2010**, *132*, 12796. (g) Xu, Z. J.; Fang, R.; Zhao, C.; Huang, J. S.; Li, G. Y.; Zhu, N.; Che, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 4405. (h) Goudreau, S. R.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 15633. (i) Kanchiku, S.; Suematsu, H.; Matsumoto, K.; Uchida, T.; Katsuki, T. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 3889. (j) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22. (k) Kim, H. Y.; Lurain, A. E.; Garcia-Carcia, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13138. (l) Chen, Y.; Fields, K. B.; Zhang, X. P. *J. Am. Chem. Soc.* **2004**, *126*, 14718. (m) Nowlan, D. T.; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902. (n) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*,

6897. (o) Davies, H. M. L.; Clark, T. J.; Church, L. A. *Tetrahedron Lett.* **1989**, *30*, 5057.
(8) Catalytic cyclopropanation by noncarbenoid mechanisms: (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (b) Dai, L.-X.; Hou, X.-L. *Pure Appl. Chem.* **1999**, *71*, 369. (c) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (d) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328.
(9) Trisubstituted alkene cyclopropanation using acceptor−acceptor carbenoids: (a) Vanier, S. F.; Larouche, G.; Wurz, R. P.; Charette, A. B. *Org. Lett.* **2010**, *12*, 672. (b) Lin, W.; Charette, A. B. *Adv. Synth. Catal.* **2005**, *347*, 1547. Tetrasubstituted alkene cyclopropanation: (c) Abe, M.; Saito, A.; Nakada, M. *Tetrahedron Lett.* **2010**, *51*, 1298. (d) White, J. D.; Torii, S.; Nogami, J. *Tetrahedron Lett.* **1974**, *15*, 2879. (e) Davies, H. M. L.; Doan, B. D. *J. Org. Chem.* **1999**, *64*, 8501. (f) Hudlicky, T.; Kwart, L. D.; Tiedje, M. H.; Ranu, B. C.; Short, R. P.; Frazier, J. O.; Rigby, H. L. *Synthesis* **1986**, *18*, 716.
(10) (a) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774. (b) Levin, S.; Nani, R. R.; Reisman, S. E. *Org. Lett.* **2010**, *12*, 780. (c) Isolation paper: Aoyagi, Y.; Yamazaki, A.; Nakatsugawa, C.; Fukaya, H.; Takeya, K.; Kawauchi, S.; Izumi, H. *Org. Lett.* **2008**, *10*, 4429.
(11) (a) Buchner, E.; Curtius, T. *Chem. Ber.* **1885**, *18*, 2377. (b) Buchner, E. *Chem. Ber.* **1896**, *19*, 106.
(12) Seminal reports of transition-metal-catalyzed Buchner reactions: (a) Anciaux, A. J.; Demonceau, A.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *Chem. Commun.* **1980**, *16*, 765. (b) Scott, L. T.; Minton, M. A.; Kirms, M. A. *J. Am. Chem. Soc.* **1980**, *102*, 6311. (c) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873.
(13) (a) Reisman, S. E.; Nani, R. R.; Levin, S. *Synlett* **2011**, *22*, 2437. (b) McNamara, O. A.; Maguire, A. R. *Tetrahedron* **2011**, *67*, 9. (c) Morris, J. C.; Mander, L. N.; Hockless, D. C. R. *Synthesis* **1998**, *30*, 455. (d) Maier, G. *Angew. Chem., Int. Ed.* **1967**, *6*, 402.
(14) Selected applications in total synthesis: (a) Frey, B.; Wells, A. P.; Rogers, D. H.; Mander, L. N. *J. Am. Chem. Soc.* **1998**, *120*, 1914. (b) King, G. R.; Mander, L. N.; Monck, N. J. T.; Morris, J. C.; Zhang, H. B. *J. Am. Chem. Soc.* **1997**, *119*, 3828. (c) Kennedy, M.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, *10*, 2565.
(15) (a) Rogers, D. H.; Morris, J. C.; Roden, F. S.; Frey, B.; King, G. R.; Russkamp, F. W.; Bell, R. A.; Mander, L. N. *Pure Appl. Chem.* **1996**, *68*, 515. (b) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (c) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (d) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, *12*, 1047. (e) McKervey, M. A.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Chem. Commun.* **1984**, 129. See also: (f) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, *35*, 1137.
(16) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.
(17) Doyle, M. P.; Shanklin, M. S.; Oon, S. M.; Pho, H. Q.; Vanderheide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384.
(18) Buchner reactions of A−A diazo substrates containing three atom linkers: (a) Park, C. P.; Nagle, A.; Yoon, C. H.; Chen, C. L.; Jung, K. W. *J. Org. Chem.* **2009**, *74*, 6231. (b) Yoon, C. H.; Nagle, A.; Chen, C. L.; Gandhi, D.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2259. (c) Whitehouse, D. L.; Nelson, K. H.; Savinov, S. N.; Lowe, R. S.; Austin, D. J. *Bioorg. Med. Chem.* **1998**, *6*, 1273. (d) Moody, C. J.; Miah, S.; Slawin, A. M. Z.; Mansfield, D. J.; Richards, I. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4067. (e) Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P.; Semones, M. A.; Padwa, A.; Richards, I. C. *Tetrahedron* **1996**, *52*, 2489. (f) Zaragoza, F. *Tetrahedron* **1995**, *51*, 8829.
(19) On the basis of our previous studies, Heinrich et al. recently reported that an α-diazo-β-ketonitrile substrate analogous to **7** but lacking the isodihydrofuran ring undergoes cyclopropanation with $Rh_2(OAc)_4$ to afford a stable norcaradiene. Heinrich, N.; Banwell, M. G.; Willis, A. C.; Cade, I. A.; Capon, R. J.; Huang, X.-C. *Aust. J. Chem.* **2012**, *65*, 1679.
(20) Manolikakes, G.; Hernandez, C. M.; Schade, M. A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 8422.
(21) (a) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2011**, *13*, 2514. (b) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797.
(22) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.
(23) For a computational analysis and comparison of C−H insertion processes by Rh- and Cu-carbenoids, see: (a) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181. This study found that the transition state energy for methane C−H insertion by a mononuclear Cu-carbenoid is significantly higher than that of a dinuclear Rh-carbenoid. For computational studies of Cu-catalyzed cyclopropanation, see: (b) Suenobu, K.; Itagaki, M.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 7271. (c) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339.
(24) Substrate **14g** (R^1 = phenyl) was also synthesized. Subjection of this compound to the standard reaction conditions provided the corresponding C−H insertion product; no cyclopropanation products were detected. This entry was omitted from Table 2 because of the difficulties in obtaining analytically pure quantities of the C−H insertion product. For examples of inter- and intramolecular C−H insertion of donor−acceptor diazo compounds, see: (a) Taber, D. F.; Tian, W. W. *J. Org. Chem.* **2007**, *72*, 3207. (b) Burgess, K.; Lim, H. J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed.* **1996**, *35*, 220. For a review, see: (c) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.
(25) For similar reactivity, see: Maguire, A. R.; O'Leary, P.; Harrington, F.; Lawrence, S. E.; Blake, A. J. *J. Org. Chem.* **2001**, *66*, 7166.
(26) For similar substituent effects observed with the terminal diazoketone, see reference 15b.
(27) (a) Zhang, B.; Wee, A. G. H. *Org. Biomol. Chem.* **2012**, *10*, 4597. (b) Wee, A. G. H.; Duncan, S. C. *J. Org. Chem.* **2005**, *70*, 8372. (c) Doyle, M. P.; Hu, W. H.; Wee, A. G. H.; Wang, Z. Y.; Duncan, S. C. *Org. Lett.* **2003**, *5*, 407. (d) Wee, A. G. H.; Duncan, S. C. *Tetrahedron Lett.* **2002**, *43*, 6173. (e) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820.
(28) Cyclopropanation of electron deficient alkenes via a concerted cycloaddition mechanism is typically disfavored with electrophilic rhodium-carbenoids; however, several other metals catalyze these reactions: (a) Chen, Y.; Ruppel, J. V.; Zhang, X. P. *J. Am. Chem. Soc.* **2007**, *129*, 12074. (b) Miller, J. A.; Jin, W.; Nguyen, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 2953. (c) Denmark, S. E.; Stavenger, R. A.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375. (d) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44. (e) Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem.* **1982**, *47*, 4059.
(29) (a) Marcoux, D.; Charette, A. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 10155. (b) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.
(30) Lindsay, V. N. G.; Fiset, D.; Gritsch, P. J.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 1463.
(31) The relative stereochemistry of the newly formed methine could not be definitively assigned by NOE experiments; however, related examples of stereospecific S_N2' reactions of cuprates would suggest the stereoisomer of **26** as shown. See: (a) Casey, C. P.; Cesa, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4236. (b) Corey, E. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1972**, *94*, 4014.
(32) The relative stereochemistry was determined by NOE analysis (see Supporting Information) and is consistent with previously reported S_N2 ring-opening of activated cyclopropanes, see reference 31.
(33) (a) Xing, S. Y.; Pan, W. Y.; Liu, C.; Ren, J.; Wang, Z. W. *Angew. Chem., Int. Ed.* **2010**, *49*, 3215. (c) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122. (b) Pohlhaus, P. D.; Sanders, S. D.;

Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642. (c) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014.
(34) Smith, A. G.; Slade, M. C.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 1996.
(35) For examples of D−A cyclopropane cycloadditions utilizing a nitrile as the acceptor moiety, see: (a) Dieskau, A. P.; Holzwarth, M. S.; Plietker, B. *J. Am. Chem. Soc.* **2012**, *134*, 5048. (b) Sliwinska, A.; Czardybon, W.; Warkentin, J. *Org. Lett.* **2007**, *9*, 695.