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Chemoselective Intramolecular Carbonyl Ylide Formation through Electronically Differentiated Malonate Diesters

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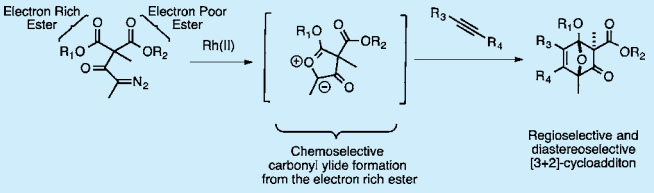
Supporting Information

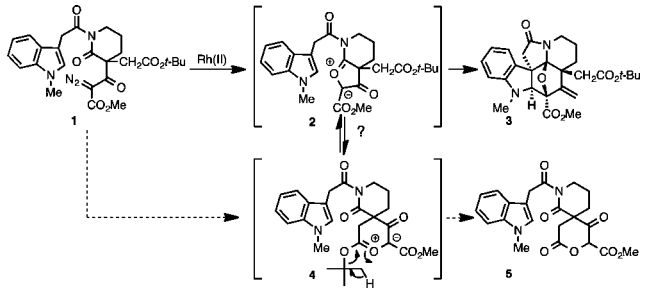
ABSTRACT: A method for chemoselective carbonyl ylide formation utilizing the Rh(II) catalyzed decomposition of electronically differentiated diazo malonates is disclosed. Treatment of ethyl, trifluoro ethyl diazo malonate with a Rh(II) catalyst selectively forms a carbonyl ylide from the relatively electron rich ethyl ester. This carbonyl ylide can be trapped by various alkynes giving highly functionalized oxabicyclic compounds in a chemo-, regio-, and diastereoselective fashion.



Over the past three decades, since the seminal work of Bien et al.,[1] rhodium(II) catalyzed carbonyl ylide formation and subsequent dipolar cycloadditions have been extensively studied and broadly utilized. The ligand induced chemoselectivity of these reactions[2−5] as well as asymmetric induction induced by chiral Rh(II) catalysts[5−8] have also been the subjects of several studies and inspired the use of these reactions as key steps in syntheses of numerous natural products,[9−18] including our own racemic synthesis of epoxysorbicillinol.[17]

Although rhodium initiated carbonyl ylide formation is driven by the electrophilic nature of the incipient rhodium carbenoid,[5,19] examples wherein this electrophilicity has been exploited in clearly differentiating between two equidistant carbonyls are unknown.[4] However, in an example taken from the extensive studies of Padwa in this area (Scheme 1) one might

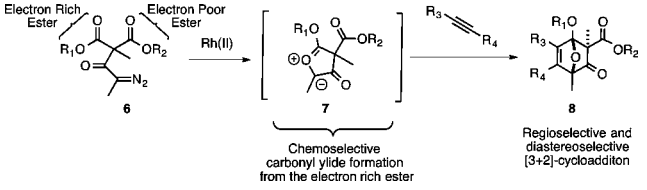
Scheme 1. Prior Studies by Padwa[20]



glean some evidence of such selectivity.[20] In this example, diazo imide **1** was observed to undergo conversion to **3** upon exposure to $Rh_2(OAc)_4$; a reaction that proceeds by way of an intermediate carbonyl ylide **2** derived from reaction of the relatively electron rich imide moiety. Product **5**, which one might expect to result rapidly from carbonyl ylide formation at the proximal *t*-Bu ester (**4**), was not observed (vide infra); however, the fact that this pathway would be kinetically less favorable makes it difficult to precisely define what dictates observed selectivity.

Herein we report that electronically differentiated diazo malonate esters (e.g., **6** Scheme 2) chemoselectively form

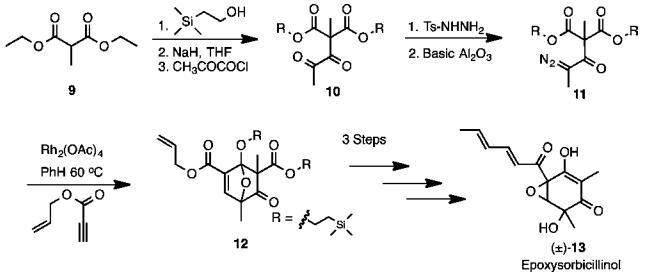
Scheme 2. Electronic Differentiation in Carbonyl Ylide Formation



carbonyl ylides (**7**) that, in turn, undergo regio- and diastereoselective cycloaddition reactions with various alkynes to furnish highly functionalized oxabicyclic compounds (**8**).

Our interest in developing a method for chemoselective differentiation of malonate esters evolved as part of an effort to implement an enantioselective total synthesis of epoxysorbicillinol **13**.[21] To this end, we sought to adapt our racemic approach (Scheme 3) through either reagent- (i.e., an asymmetric catalyst) or substrate-controlled desymmetrization in the cycloaddition

Scheme 3. Racemic Synthesis of Epoxysorbicillinol[21]



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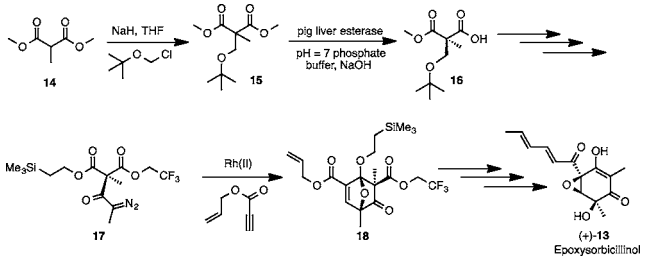
step (**11** → **12**). While the former of these approaches would take advantage of the symmetric intermediate (**11**),[22] the latter would require desymmetrization of the esters (e.g., via sterics or electronics) and subsequent selective carbonyl ylide formation upon exposure of the now chiral malonate to Rh-promoted cylcoaddition (cf., **6** → **8** and **11** → **12**).

As illustrated in Scheme 4, we envisioned that enzymatic desymmetrization of an intermediate malonate (i.e., **15** → **16**)

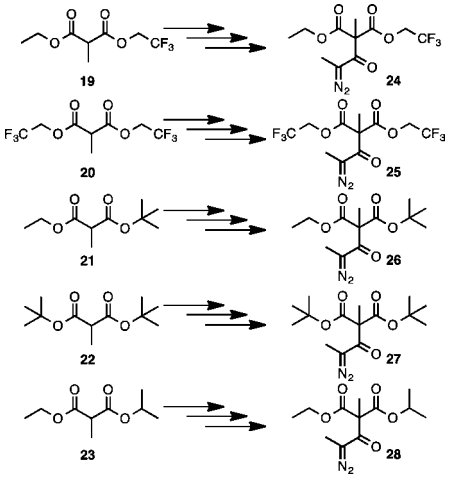
Scheme 4. Asymmetric Synthesis of (+)-Epoxysorbicillinol[21]



followed by re-esterification with an electronic or sterically modified alcohol would furnish a chiral intermediate (e.g., **17**), which, provided that the ester differentiation is manifest in the cycloaddition chemistry, would selectively furnish an intermediate (**18**) poised for completing the enantioselective synthesis.

Thus, our studies began with the preparation of malonates **19**−**23**. Subsequent acylation and conversion to the corresponding diazoketones **24**−**28** (Scheme 5) set the stage for exploring

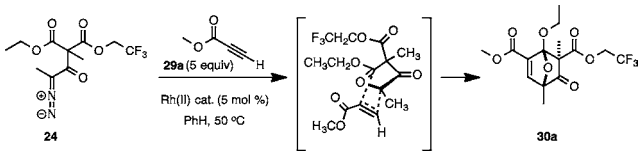
Scheme 5. Preparation of Diazo Malonates 24-28



the cycloaddition chemistry.[23] In the event, our initial studies focused on the reaction of electronically differentiated substrate **24** (Table 1) with methyl propiolate **29a**. We were delighted to discover that this reaction provides oxabicycle **30a** as the only isolable product in 58% yield, presumably via chemoselective ylide formation. The regio- and diastereoselectivity observed in product **30a** are consistent with the intrinsic polarization of the dipole/dipolarophile and reaction through the illustrated transition structure (Table 1) wherein one face of the dipole is blocked by the ester.[24]

Encouraged by our initial success, we sought to optimize the reaction conditions. A screening of catalysts established that electron withdrawing ligands are detrimental and the corresponding reactions furnish no desired oxabicyclic products (Table 1, entries 4 and 5). As expected, the octanoate ligand behaved similarly to acetate (Table 1, entries 2 and 3), and both of the latter catalysts were found to furnish improved yields (71%) upon extending the reaction time to 24 h. The relative ease of purification accompanying reactions run with rhodium acetate led to our selecting this catalyst for use in subsequent reactions.

Table 1. Screening of Rhodium Catalysts[a]

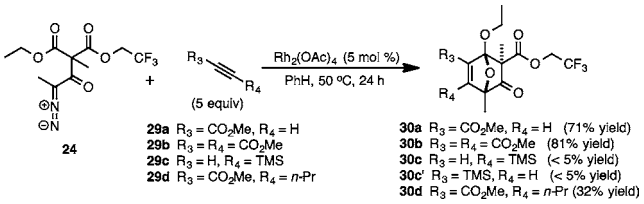


entry	catalyst	time	yield[b]
1	$Rh_2(OAc)_4$	12 h	58%
2	$Rh_2(OAc)_4$	24 h	71%
3	$[Rh[Oct]_2]_2$	24 h	71%
4	$[Rh[TFA]_2]_2$	24 h	0%
5	$[Rh(pfb)_2]_2$	24 h	0%

[a]General conditions: **4a** (0.16 mmol), **5a** (5 equiv), Rh(II) cat. (5 mol %), PhH (1.5 mL), 50 °C, 12−24 h. [b]Yields reported are of material isolated by silica gel chromatography.

To determine the impact, if any, of the dipolarophile on chemoselectivity we screened the cycloaddition of **24** with **29a**−**d** (Scheme 6). We noted that with all substrates, electron poor

Scheme 6. Affect of Dipolarophile upon Chemoselectivity[a,b]



[a]Yields reported are of material isolated by silica gel chromatography. [b]Product **30c**/**c**′ forms as a 3:1 mixture of regioisomers, respectively, as observed via ^{1}H NMR of the crude reaction mixture.

(e.g., **29a**/**b**) or relatively electron rich (e.g., **29c**/**d**), the chemo- and diastereoselectivity observed with the original substrate combination is preserved. As expected of a type I dipole, electron deficient alkynes **29a**/**b** were better reaction partners giving 71% and 81% yield, respectively. Additionally, the reaction with TMS-acetylene produced only trace amounts of two products (3:1), which have been tentatively assigned as regioisomers **30c**/**c**′, respectively.[21,25]

Having observed consistent chemoselectivity, we next explored the ability of electron deficient esters to engage in carbonyl ylide formation and thus exposed bis-trifluoroethyl malonate **25** to the cycloaddition conditions (Scheme 7). Interestingly under our standard reaction conditions, **25** was found to produce the oxabicycle **31** in 58% yield. This result supports the notion that the chemoselectivity observed in reactions of **24** results from preferential ylide formation and not differential reactivity of the derived carbonyl ylides.[26]

Given that electronic effects were found to be capable of providing excellent chemoselectivity, we next attempted to achieve a similar result using sterically differentiated esters. To this end we explored reactivity of the isopropyl and *t*-butyl

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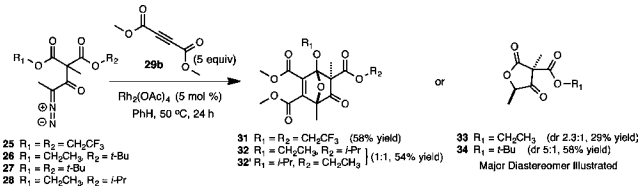
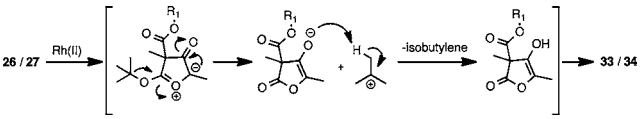
Scheme 7. Variation of Malonate Sterics and Electronics[a,b]



[a]Yields reported are of material isolated by silica gel chromatography. [b]Isomeric ratios determined by ^{1}H NMR of crude material.

variants, **26**–**28** (Scheme 7). Interestingly, attempted cycloadditions between **26**/**27** and **29b** under our standard reaction conditions failed to produce any oxabicyclic products. Instead, tetronic acids **33** and **34** were isolated as 2.3:1 and 5:1 mixtures of diastereomers, respectively; a result which we attribute to rapid loss of the *t*-butyl moiety from the intermediate carbonyl ylide (Scheme 8).[27] As expected, these unimolecular decomposition products are also produced in reactions wherein the alkyne component is omitted from the mixture.

Scheme 8. Mechanism of Tetronic Acid Formation



The lability of the *t*-Bu esters led us to next explore the corresponding *i*-Pr substrate **28**. Surprisingly, the reaction of **28** with **29b** yielded a 1:1 mixture of isomeric cycloadducts **32**/**32′** indicating that in these systems steric differentiation is not a viable approach for translating stereochemistry.[28,29]

In summary, we have herein established that electronic differentiation can be employed to direct the course of rhodium catalyzed carbonyl ylide formation. This simple method enables translation of stereochemistry and has been demonstrated to produce carbonyl ylides that undergo highly regio- and diastereoselective dipolar cycloaddition reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02847.

Experimental procedures and spectral data for all new compounds (PDF)
Compound **30b** (CIF)
Compound **31** (CIF)
Compound **34** (CIF)

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Notes

The authors declare no competing financial interest.

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(21) For additional examples, see: Lee, C.-W. The Formal Asymmetric Synthesis of (+)-Epoxysorbicillinol. Ph.D. Thesis, Yale University, New Haven, CT, 2005.
(22) (a) Although feasibility of the catalytic approach is supported by several elegant examples of catalytic entantioselective carbonyl ylide cycloadditions,[21] we chose to direct our initial efforts on substrate control. (b) Hanari, T.; Kurosaki, Y.; Thrimurtulu, N.; Nambu, H.; Anada, M.; Hashimoto, S.; Shimada, N. *Chem. - Eur. J.* **2015**, *21*, 11671. (c) Suga, H.; Hashimoto, Y.; Yasumura, S.; Takezawa, R.; Itoh, K.; Kakehi, A. *J. Org. Chem.* **2013**, *78*, 10840.
(23) For details describing the synthesis of the malonates **19**–**23** and the diazo ketones **24**–**28**, refer to the Supporting Information and references therein.
(24) Conformational analysis using simple MM2 calculations support the notion that diastereoface selectivity derives from steric biases present in the transition structure illustrated in Table 1. The relative

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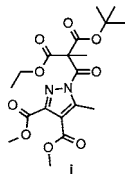
stereochemistry of **30a** was assigned by analogy to **30b**, the structure of which was unambiguously confirmed via single crystal X-ray analysis.

(25) Due to the low yield, full characterization of an analytically pure sample of the TMS-acetylene derived products (**30c**/**c**′) were not possible. However, ^{1}H NMR, ^{13}C NMR, and HMBC of the impure product were consistent with the indicated structures.

(26) In an effort to gain insight into the relative rates of these reactions, a competition experiment was preformed wherein a 1:1 mixture of substrates **24** and **25** was exposed to the reaction conditions using methyl propiolate as the dipolarophile. Monitoring progress of this reaction by NMR of aliquots revealed that formation of the oxabicyclic products derived from both substrates occurs at similar rates. Thus, the chemoselectivity observed for substrate **24** derives from either selective ylide formation or rapid equilibration to the electron rich ylide prior to cycloaddition.

(27) The relative configuration assigned to the major (illustrated) diastereomer of **34** was determined via single crystal X-ray analysis.



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(28) In contrast to the *t*-butyl malonates, exposure of **28** to $Rh_2(OAc)_2$ in the absence of a dipolarophile does not furnish tetronic acid products.

(29) (a) Notably, the reactions of **26**−**28** were found to produce trace amounts of a side product, which we believed to be a pyrazole. To explore this notion, **26** and **29b** were exposed to our standard reaction conditions in the absence of the rhodium catalyst. Under these conditions pyrazole **i** is produced in 96% yield. Previous investigations from Neumann suggest that these products derive from initial formation of a pyrazolenine through a dipolar cycloaddition, which is followed by a thermal 1,5-acyl shift and aromatization.[29b]. (b) Neumann, M. F.; Buchecker, C. D. *Tetrahedron Lett.* **1976**, *24*, 2069. (c) For a very recent preparation of pyrazoles from diazo-containing precursors, see: Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 13729.

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