Pericyclic Rearrangement

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Preparation of α-Oxygenated Ketones by the Dioxygenation of Alkenyl Boronic Acids**

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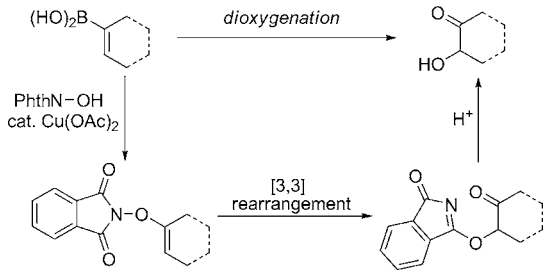
The ubiquitous use of aryl, alkenyl, and alkyl boronic acids for the formation of new C–C, C–N, and C–O bonds in cross-coupling reactions is indicative of the importance of these compounds in organic synthesis.[1] Although the use of boronic acids for the preparation of a variety of new bonds is well established, we were interested in testing if the reactivity of alkenyl boronic acids could be further diversified to include dioxygenation and the synthesis of α-oxygenated ketones. The conversion of alkenyl boronic acids to α-oxygenated ketones would provide a unique retrosynthetic disconnection for the preparation of complicated targets containing these challenging motifs.[2–8] Towards the goal of alkenyl boronic acid dioxygenation, we hypothesized that etherification of an alkenyl boronic acid with *N*-hydroxyphthalimide would form an *N*-enoxyphthalimide poised to undergo a [3,3] rearrangement to give an α-oxygenated ketone (Scheme 1). This method would avoid the use of

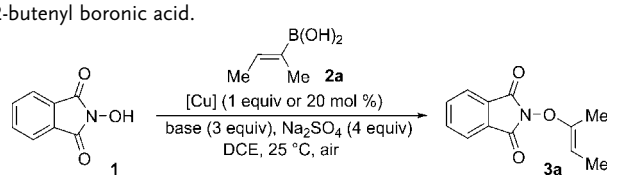


Scheme 1. Dioxygenation of alkenyl boronic acids. OAc = acetate, PhthN = phthalimide.

highly reactive electrophilic oxygenation reagents, not require the preparation of α-halogenated precursors, and allow access to linear α-oxygenated ketones from internal alkynes.[4,5d,7–9] Moreover, the nature of the transition state of the pericyclic reaction would allow for potential diastereoselective construction of the α-oxygenated stereocenter. Herein, we describe the development of a new method for the dioxygenation of alkenyl boronic acids through a copper-mediated etherification of *N*-hydroxyphthalimide followed by a [3,3] rearrangement to provide α-hydroxy or α-benzoyloxy ketones in two high-yielding steps from simple starting materials.

Our efforts towards achieving the dioxygenation of alkenyl boronic acids began with the optimization of conditions for the cross-coupling of alkenyl boronic acids and *N*-hydroxyphthalimide to form *N*-enoxyphthalimides. Although the copper-mediated arylation of *N*-hydroxyphthalimide with aryl boronic acids is known, to the best of our knowledge, the corresponding process for vinylation has not yet been reported.[10–12] Mixtures of copper salts, bases, and dessicants, as well as equivalents of reagents, were screened for their effectiveness in promoting the desired coupling of **1** and **2a**. As shown in entries 1–4 of Table 1, the use of 2 equiv of boronic acid **2a** provided a higher yield of **3a** for both copper-mediated and copper-catalyzed transformations, although the difference in reaction efficiency was more striking for the catalytic process.[13] The greater sensitivity of the catalytic reaction to changes in reaction conditions was consistent throughout the optimization process and guided our inquiry. $Cu(OAc)_2$ (OAc = acetate) was shown to be the

Table 1: Optimization of the etherification of *N*-hydroxyphthalimide with 2-butenyl boronic acid.



Entry	[Cu]	[**2a**]	Base	Yield [%] of **3a**[a]
1	$Cu(OAc)_2$ (1 equiv)	1 equiv	pyridine	71
2	$Cu(OAc)_2$ (1 equiv)	2 equiv	pyridine	96
3	$Cu(OAc)_2$ (20 mol%)	1 equiv	pyridine	6
4	$Cu(OAc)_2$ (20 mol%)	2 equiv	pyridine	87
5	CuCl (20 mol%)	2 equiv	pyridine	7
6	CuI (20 mol%)	2 equiv	pyridine	78
7	$Cu(TFA)_2$ (20 mol%)	2 equiv	pyridine	61
8	$Cu(OTf)_2$ (20 mol%)	2 equiv	pyridine	8
9	CuTC (20 mol%)	2 equiv	pyridine	81
10	$Cu(OAc)_2$ (20 mol%)	2 equiv	NEt_3	68
11	$Cu(OAc)_2$ (20 mol%)	2 equiv	DABCO	NR
12	$Cu(OAc)_2$ (20 mol%)	2 equiv	imidazole	NR
13	$Cu(OAc)_2$ (20 mol%)	2 equiv	KO*t*Bu	NR

[a] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard; NR = no reaction. DABCO = 1,4-diazabicyclo[2.2.2]octane, DCE = 1,2-dichloroethane, OAc = acetate, TC = 2-thiophenecarboxylate, Tf = trifluoromethanesulfonate, TFA = trifluoroacetate.

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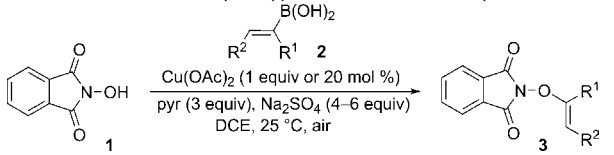
optimal catalyst when compared to other Cu^{I} and Cu^{II} salts (entries 5–9) and pyridine was shown to be the optimal base when compared to other amines and inorganic bases (entries 10–13). Neither the copper-mediated nor the copper-catalyzed coupling reaction showed any conversion to the desired product when run in the absence of air, and both transformations required the use of a halogenated solvent. The cross-coupling process was fairly insensitive to the choice of desiccant; 4 Å molecular sieves and $MgSO_4$ gave the desired product in only slightly attenuated yields.[14] The optimization study concluded that treatment of a 1:2 mixture of **1**/**2a** in 1,2-dichloroethane (DCE) with $Cu(OAc)_2$ (1 equiv or 20 mol%), pyridine (3 equiv), and Na_2SO_4 (4 equiv) in air provided optimal conversion of **2a** to **3a**.

With the optimal conditions for the cross-coupling of **1** and **2a** in hand, the scope of the transformation was evaluated with a variety of alkenyl boronic acids to determine the tolerance for boronic acid substitution patterns. As shown in Table 2, both copper-mediated and copper-catalyzed conditions converted 1- and 2-*trans*-substituted vinyl boronic acids, *Z*-disubstituted alkenyl boronic acids, and cyclic alkenyl boronic acids to the desired *N*-enoxyphthalimides **3** with retention of alkene geometry.[15] Both alkyl- and aryl substituents were tolerated for the boronic acid coupling partner, as were common aryl electron-withdrawing functional groups such as nitro, fluoro, and trifluoromethyl, as well as common protecting groups such as ketals. Trisubstituted alkenyl boronic acids and alkenyl boronic acids with *ortho*-substituted aryl groups currently represent a limitation of this method. Unfavorable steric interactions also hinder the etherification of 6-methyl cyclohexenyl boronic acid **2r**; however, no similar inhibition was observed for the fused system **2v**. The broad scope of the copper-mediated cross-coupling of *N*-hydroxyphthalimide **1** and alkenyl boronic acids **2** ultimately provided an array of *N*-enoxyphthalimides **3** to screen for the [3,3] rearrangement.

Solutions of *N*-enoxyphthalimides **3** in C_6D_6 or toluene were heated at 80–90 °C for 10–16 h to promote a [3,3] rearrangement and afford dioxygenated alkenyl boronic acids as imidates **4**. These rearrangements occurred in almost quantitative yields, as determined by comparison to an internal standard by ^{1}H NMR spectroscopy; however, imidates **4** were unstable when subjected to silica gel chromatography.[16] Isolation and purification of α-hydroxy ketones **5** was achieved in high yield after the hydrolysis of crude samples of **4** (Table 3). An ion-exchange resin provided optimal yields for the cleavage of phthalimide from **4**, but silica gel was similarly effective with longer reaction times. α-Hydroxyketones **5** that were too volatile or hydrophilic to be separated from phthalimide by extraction were protected in solution and isolated as the corresponding α-benzoyloxy ketones **6** (Table 3). The *N*-enoxyphthalimides **3b**–**3d**, underwent rearrangements to form α-oxygenated aldehydes **4b**–**4d**, which were isolated without further purification as the

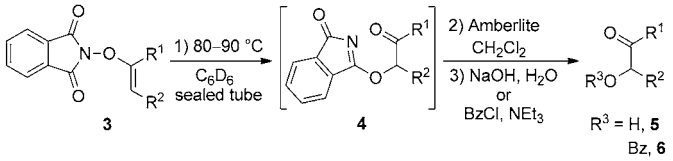
Table 2: Scope of the etherification of *N*-hydroxyphthalimide with alkenyl boronic acids.



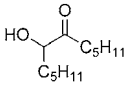
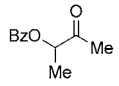
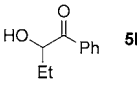
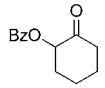
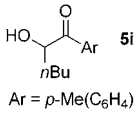
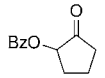
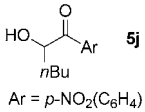
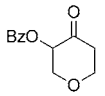
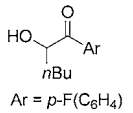
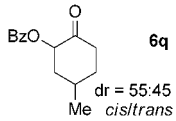
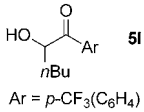
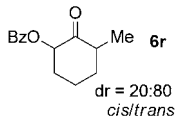
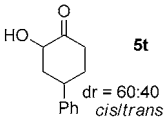
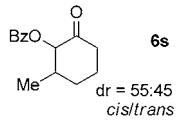
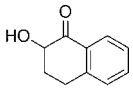
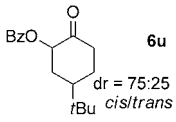
Entry	Product	Yield [%] of **3**[a]	Entry	Product	Yield [%] of **3**[a]
1	PhthN–O, Me, Me **3a**	98[b] (76)	12	PhthN–O, Ar, *n*Bu **3l** Ar = *p*-$CF_3(C_6H_4)$	82 (73)
2	PhthN–O, *n*Bu **3b**	81 (70)	13	PhthN–O **3m**	83 (76)
3	PhthN–O, Cy **3c**	87 (74)	14	PhthN–O **3n**	73 (68)
4	PhthN–O, Ph **3d**	88 (78)	15	PhthN–O, O **3o**	91 (89)
5	PhthN–O, C_5H_{11}, C_5H_{11} **3e**	81 (77)	16	PhthN–O, O, O **3p**	86 (82)
6	PhthN–O **3f**	47	17	PhthN–O, Me **3q**	84 (78)
7	PhthN–O, Ph **3g**	86 (77)	18	Me, PhthN–O **3r**	41
8	PhthN–O, Ph, Et **3h**	76 (67)	19	PhthN–O, Me **3s**	86 (80)
9	PhthN–O, Ar, *n*Bu **3i** Ar = *p*-$Me(C_6H_4)$	63 (66)	20	PhthN–O, Ph **3t**	64
10	PhthN–O, Ar, *n*Bu **3j** Ar = *p*-$NO_2(C_6H_4)$	67 (55)	21	PhthN–O, *t*Bu **3u**	83
11	PhthN–O, Ar, *n*Bu **3k** Ar = *p*-$F(C_6H_4)$	70 (71)	22	PhthN–O **3v**	76 (52)

[a] Yield of isolated product using 1 equiv $Cu(OAc)_2$ and (yield of isolated product using 20 mol% $Cu(OAc)_2$). [b] When run on a 1 mmol scale, the yield of isolated product using 1 equiv of $Cu(OAc)_2$ was 74%. Cy = cyclohexyl, DCE = 1,2-dichloroethane, PhthN = phthalimide, OAc = acetate, pyr = pyridine.

Table 3: Preparation of α-hydroxy- and α-benzoyloxyketones by rearrangement and hydrolysis of *N*-enoxyphthalimides **3**.



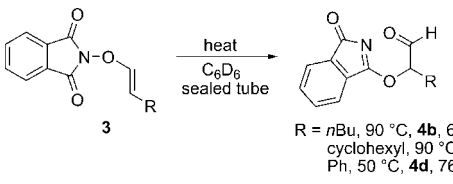
3 **4**

Entry	Product	Yield [%] of **5**[a]	Entry	Product	Yield [%] of **6**[a]
1	 **5e**	78[b]	9	 **6a**	86
2	 **5h**	90[b]	10	 **6m**	67
3	 **5i** Ar = *p*-Me(C_6H_4)	82	11	 **6n**	66
4	 **5j** Ar = *p*-NO_2(C_6H_4)	75	12	 **6o**	69
5	 **5k** Ar = *p*-F(C_6H_4)	88	13	 **6q** dr = 55:45 *cis*/*trans*	65
6	 **5l** Ar = *p*-CF_3(C_6H_4)	86	14	 **6r** dr = 20:80 *cis*/*trans*	66
7	 **5t** dr = 60:40 *cis*/*trans*	82	15	 **6s** dr = 55:45 *cis*/*trans*	69
8	 **5v**	87	16	 **6u** dr = 75:25 *cis*/*trans*	66

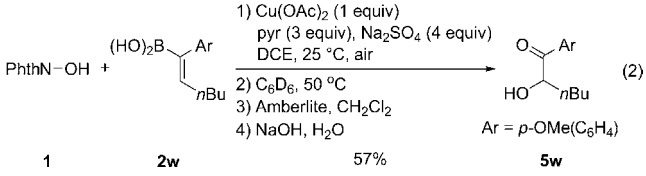
[a] Yield of isolated product. [b] Hydrolysis promoted with SiO_2. Bz = benzoyl, Amberlite = Amberlite IR120H, ion-exchange resin.

corresponding imidates to avoid polymerization of the corresponding α-hydroxy aldehydes [Eq. (1)]. The products shown in Table 3 and equation 1 describe the broad scope of α-oxygenated carbonyl compounds that can be prepared from the dioxygenation of alkenyl boronic acids with *N*-hydroxyphthalimide **1** through the rearrangement of *N*-enoxyphthalimides **3**. This method provides a valuable alternative to known procedures, which originate from ketone or aldehyde starting materials and employ electrophilic sources of oxygen.

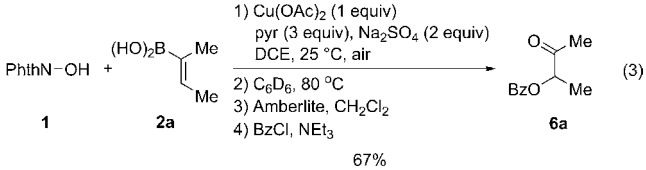
Several aryl-substituted *N*-enoxyphthalimides exhibited exceptions to the general thermal reactivity patterns depicted in Table 3 and equation 1 that suggested trends in the [3,3] rearrangement activity of these compounds. *N*-Enoxyphthalimide **3d** readily formed **4d** when heated to only 50 °C [Eq. (1)]. This transformation is in contrast to **3b** and **3c**, which rearranged at 90 °C, and **3g**, which exhibited no rearrangement reactivity even when heated to 130 °C. The combination of an aryl group at the 1-position of *N*-enoxyphthalimides **3h–3l**, and an alkyl group at the 2-position attenuated the opposing affects observed for **3d** and **3g**, and the rearrangements to afford **4h–4l** occurred at 80 °C (Table 3); however, the addition of an electron-donating group to the aryl ring once again reduced the rearrangement temperature to 25–50 °C to give **5w** [Eq. (2)]. *N*-Enoxyphthalimide **3w** could not be isolated, as the copper-mediated coupling provided a 2:1 mixture of **3w**/**5w**. Filtration of this mixture through silica gel to remove $Cu(OAc)_2$, followed by warming to 50 °C for 10 h and hydrolysis, gave **5w** in 57 % yield over three steps. A similarly efficient process was also observed for the transformation of **2a** to **6a** in 67 % yield with no formal purification of intermediates, only the removal of $Cu(OAc)_2$ prior to rearrangement [Eq. (3)].



3 (1)



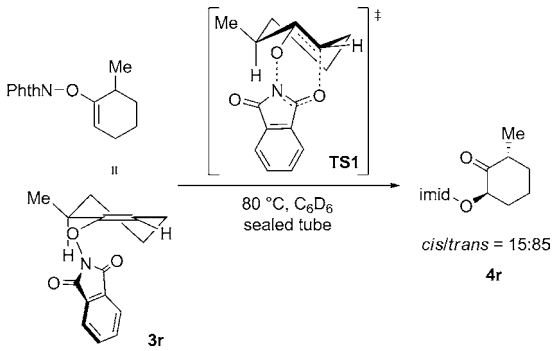
1 **2w** **5w** (2)



1 **2a** **6a** (3)

$Cu(OAc)_2$ can be present in substoichiometric amounts during the rearrangement of **3a**, but attenuated yields of **4a** are obtained. These results show that the [3,3] rearrangement of **3** is inhibited by the presence of copper salts and facilitated by electron-donating aryl groups at the 1-position and phenyl substituents at the 2-position of the enol ether.

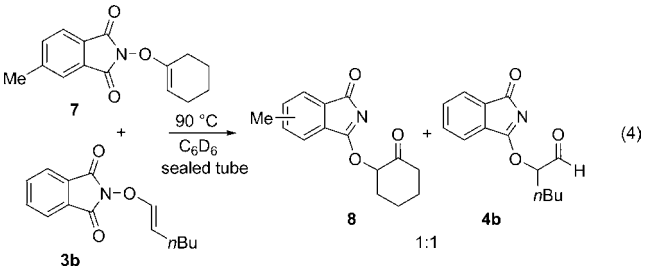
The diastereoselectivity of the [3,3] rearrangement of *N*-enoxyphthalimides was tested using *N*-enoxyphthalimides **3q**–**3u**, which are derived from substituted cyclohexenyl boronic acids. Compounds **3q**, **3s**, **3t**, and **3u** underwent [3,3] rearrangements to give 50:50 to 60:40, *cis*/*trans* diastereomeric mixtures of **4** and subsequent hydrolysis to give **6q**, **6s**, and **5t** with no significant change in the diastereomeric ratio (Table 3). Hydrolysis and protection of **4u** epimerized the α-benzoyl group, resulting in a 75:25 mixture of *cis*/*trans* **6u** (Table 3). Surprisingly, the rearrangement of **3r** strongly favors formation of the *trans* diastereomer (Scheme 2). We



Scheme 2. Diastereoselective rearrangement of **3r** to **4r**.

assume that this result is due to minimization of steric interactions as the rearrangement occurs via a chair transition state (**TS1**). In contrast to 4-substituted cyclohexenyl substrates **3q**, **3s**, and **3u**, rotation to give an approach of the carbonyl oxygen from the higher energy twist conformation and provide the *cis* diastereomer is inaccessible for **3r** because of the 6-methyl substituent, which inhibits rotation of the *N*-enoxyphthalimide around the C–O bond. A moderate increase in the *cis*/*trans* ratio from 15:85 to 20:80 was observed upon hydrolysis and protection of **4r**. To the best of our knowledge, the diastereomeric ratio observed for **4r** represents the highest observed in favor of the *trans* isomer for 2-methylcyclohexanone α-oxygenation.[4d,17] This implies that the dioxygenation of alkenyl boronic acids may not only provide a new retrosynthetic disconnection for the preparation of α-oxygenated carbonyl compounds, but also access to relative stereochemical patterns not readily available through enolate oxidation procedures.

The diastereoselectivity observed for the rearrangement of **3r** suggested that the [3,3] rearrangements of *N*-enoxyphthalimides proceed by a unimolecular pericyclic reaction. The intramolecular nature of the transition state was further supported by a crossover experiment using *N*-enoxyphthalimides **3b** and **7** [Eq. (4)]. When a 1:1 mixture of these compounds was heated in C_6D_6 at 90 °C for 18 h, only **4b** and **7** were observed and there was no evidence of crossover by ^1H



(4)

or ^{13}C NMR spectroscopy. To investigate the possibility of a radical reaction pathway, a radical clock experiment was tested with *N*-enoxyphthalimide **3f**. Upon heating **3f** in either the presence or the absence of Bu_3SnH, no indication of the formation of an α,β-unsaturated aldehyde was observed, suggesting that the [3,3] rearrangement occurs through a two-electron pathway.

In summary, we have shown that dioxygenation of alkenyl boronic acids **2** with *N*-hydroxyphthalimide **1** can be achieved by a two-step process involving copper-mediated etherification to form an *N*-enoxyphthalimide **3** and a subsequent [3,3] rearrangement to provide α-hydroxy ketones **5** or α-benzoyloxy ketones **6**, after hydrolysis of the phthalimide imidate. This transformation provides a new retrosynthetic disconnection for the preparation of α-oxygenated carbonyl compounds that does not require the use of a highly reactive electrophilic oxygen source or a carbonyl compound as a starting material. Ongoing work in our laboratory is focused on further exploring the synthetic utility of this transformation and exploiting the observed diastereoselectivity.

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[15] Alkene geometry was retained and products **3** were isolated as *E* alkenes within the limits of detection by ^{1}H NMR spectroscopy.

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