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Highly Selective Catalyst-Dependent Competitive 1,2-C→C, -O→C, and -N→C Migrations from β-Methylene-β-silyloxy-β-amido-α-diazoacetates

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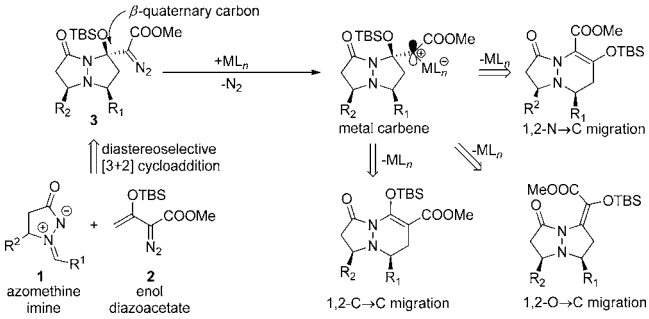
Supporting Information

ABSTRACT: Transition-metal catalysts direct 1,2-C→C, -O→C, and -N→C migrations from β-methylene-β-silyloxy-β-amido-α-diazoacetates with high selectivity. The key to achieving this unique display of differential selectivities relies on steric and stereoelectronic control by their catalytically generated metal carbenes.

1,2-Migration to an electrophilic carbon center is a common transformation in organic chemistry that has been widely investigated for its intriguing mechanistic features[1] and extensive occurrence in catalysis.[2] Among the reactions that encompass these 1,2-migrations are the semipinacol rearrangement and its multiple variants[3] and solvolysis reactions,[1d] which include Wagner−Meerwein rearrangements,[4] ring-enlargement reactions,[5] and, more recently, gold-catalyzed migrations.[6] With free rotation around the C−C bond to the electrophilic carbon, group migration is dependent upon the migratory aptitude as well as the spatial positioning of the migrating group relative to the electrophilic center.[1a,b,4a,c] In general, although highly selective migrations are most desirable, competition between two migrating groups is commonly observed.[1c,5b,c] In these reactions, the product that is formed is dependent on the structure of the reactant,[4a,b,e] and external control of which group migrates has long been problematic.[3,4] Catalytically generated metal carbenes from α-diazo carbonyl compounds are highly electrophilic, and 1,2-migration occurs when a saturated carbon is directly bonded to the carbene center.[7] However, examples of catalyst-controlled migrations are rarely encountered,[8] and effective catalyst-controlled selectivity in these transformations remains unsolved.[9]

We have been intrigued by catalyst control of reaction outcomes emanating from the same reactants, and we have previously presented diverse catalyst-dependent outcomes from reactions of enol diazoacetates with α,β-unsaturated aldehydes[10] and nitrones.[11] We asked the question "could a catalytically generated metal carbene intermediate with an adjacent saturated carbon atom having three different substituents be induced by different catalysts to undergo selective 1,2-migration of each of the substituents?" To answer this question, obtaining facile access to α-diazo compounds bearing β-quaternary carbons was our first objective. Inspired by our recent efforts in using enol diazoacetates in Lewis acid-catalyzed reactions,[12] we envisioned that the construction of α-diazo compounds could be accomplished by [3 + 2] cycloaddition of dipolar species and an enol diazoacetate (Scheme 1). Azomethine imines appeared to be promising candidates since they are stable, easily accessible dipolar

Scheme 1. Strategy for the Synthesis of α-Diazoacetates Bearing β-Quaternary Carbons and Chemoselectivity of Competitive 1,2-C→C, -O→C, and -N→C Migrations



compounds and precursors for the synthesis of dinitrogen-fused heterocyclic rings,[13] which display broad biological activities.[14] As expected, the synthesis of the aforementioned α-diazoacetates was achieved by diastereoselective [3 + 2] cycloaddition reactions of azomethine imines **1** with enol diazoacetate **2** under Lewis acid catalysis. The β-quaternary carbon is directly bound to carbon, nitrogen, and oxygen substituents that are poised to rearrange to an adjacent electrophilic carbon. Herein we report that different metal catalysts direct the migration by carbon, nitrogen, and oxygen substituents with a high degree of selectivity to generate a diverse array of highly functionalized fused-ring heterocyclic compounds in an efficient and controllable manner.

We initiated our study of the Lewis acid-catalyzed reaction between azomethine imines **1** (R^2 = H) and enol diazoacetate **2** by using $Sc(OTf)_3$ (Table 1, entries 1−7). Highly diastereoselective [3 + 2] cycloaddition occurred with the pendant phenyl and TBSO groups cis to each other, as confirmed by X-ray diffraction (XRD) analysis. Further investigations with 5-phenylazomethine imines **1** (R^2 = Ph) revealed that $In(OTf)_3$ afforded a higher level of diastereoselectivity than $Sc(OTf)_3$ (entries 8−13). Azomethine imines containing electron-withdrawing (entries 3, 9, 11, and 12) and electron-donating (entries 2, 4, 5, and 10) substituents on the phenyl rings afforded the desired products in high isolated yields.

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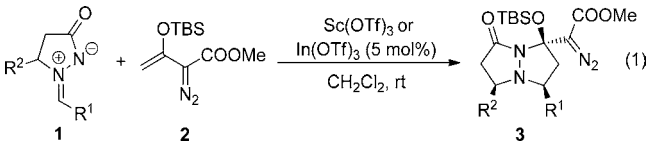
Table 1. Lewis Acid-Catalyzed Diastereoselecive [3 + 2] Cycloaddition of Azomethine Imines 1 with Enol Diazoacetate 2



1 2 3

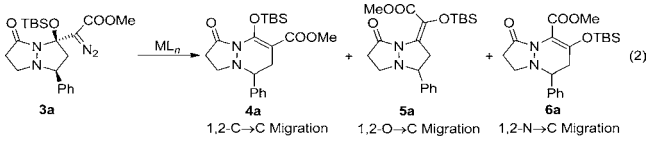
entry[a]	R^1	R^2	3[d]	yield (%)[e]
1[b]	Ph	H	**3a**	90
2[b]	4-MeC_6H_4	H	**3b**	74
3[b]	4-ClC_6H_4	H	**3c**	78
4[b]	2-$MeOC_6H_4$	H	**3d**	65
5[b]	4-$MeOC_6H_4$	H	**3e**	69
6[b]	cyclohexyl	H	**3f**	80
7[b]	(*E*)-Ph−CH═CH	H	**3g**	67
8[c]	Ph	Ph	**3h**	81
9[c]	4-$NO_2C_6H_4$	Ph	**3i**	66
10[c]	4-$MeOC_6H_4$	Ph	**3j**	71
11[c]	4-BrC_6H_4	Ph	**3k**	78
12[c]	3-BrC_6H_4	Ph	**3l**	72
13[c]	cyclohexyl	Ph	**3m**	56

[a]Reactions were performed with 0.25 mmol of **1** (1.0 equiv) and **2** (1.8 equiv) in CH_2Cl_2 for 12 h at room temperature. [b]5 mol % $Sc(OTf)_3$ used as the catalyst. [c]5 mol % $In(OTf)_3$ used as the catalyst. [d]A single diastereomer was obtained. [e]Isolated yields.

Furthermore, substituents at the para (entries 2−3, 5, and 9−11), meta (entry 12), and ortho (entry 4) positions on the phenyl rings were well-tolerated. Azomethine imines derived from cinnamaldehyde (entry 7) and cyclohexylcarboxaldehyde (entries 6 and 13) showed reactivity profiles similar to those derived from aromatic aldehydes, and all of the substrates shown in Table 1 afforded the cycloaddition products with complete diastereocontrol.

Having prepared highly functionalized α-diazoacetates **3** bearing quaternary carbons at the β-positions, we next investigated their transition-metal-catalyzed dinitrogen extrusion and subsequent rearrangement of the catalytically generated metal carbene intermediate (Table 2). In the reaction of **3a** with $Rh_2(OAc)_4$, three products were obtained in 90% combined yield (eq 2), and these were determined by XRD and/or spectroscopic analysis to be those from 1,2-C→C migration (**4a**, 58%), stereoselective 1,2-O→C migration (**5a**, 25%), and 1,2-N→C migration (**6a**, 17%). Using the more Lewis acidic $Rh_2(tfa)_4$ (entry 2) and $Rh_2(pfb)_4$ (entry 3) under the same conditions showed that the 1,2-N→C migration pathway was inhibited in favor of the 1,2-C→C and -O→C migrations with approximately 3:1 selectivity. In contrast, performing this reaction with the less Lewis acidic $Rh_2(cap)_4$ in $ClCH_2CH_2Cl$ at 80 °C revealed that both the 1,2-N→C and -O→C migration pathways were suppressed and 1,2-C→C migration was dominant (entry 4). In a control experiment where the same reaction was conducted with $Rh_2(OAc)_4$ under conditions otherwise identical to those with $Rh_2(cap)_4$ (entry 5), the selectivity was comparable to that for the reaction performed in CH_2Cl_2 at 40 °C (entry 1) and much lower than that with $Rh_2(cap)_4$ (entry 4). The use of $Rh_2(piv)_4$ and $Rh_2(esp)_2$ containing sterically bulky ligands gave high selectivities for both 1,2-N→C and -O→C migrations (entries 6 and 7). In contrast, copper and silver catalysts displayed distinctive and virtually exclusive selectivity for 1,2-N→C

Table 2. Catalyst Screening with 3a for Selective 1,2-C→C, -O→C, and -N→C Migrations



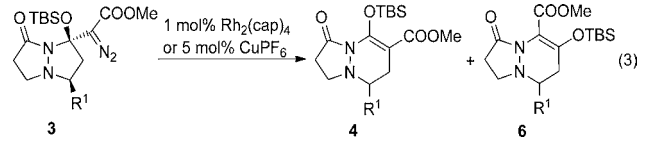
entry[a]	catalyst	temp	solvent	time (h)	4a:5a[d]:6a[e]	yield (%)[f]
1[b]	$Rh_2(OAc)_4$	40 °C	CH_2Cl_2	3	58:25:17	90
2[b]	$Rh_2(tfa)_4$	40 °C	CH_2Cl_2	3	78:22:−	94
3[b]	$Rh_2(pfb)_4$	40 °C	CH_2Cl_2	3	71:29:−	91
4[b]	$Rh_2(cap)_4$	80 °C	$(CH_2Cl)_2$	3	78:9:13	93
5[b]	$Rh_2(OAc)_4$	80 °C	$(CH_2Cl)_2$	3	61:25:14	85
6[b]	$Rh_2(piv)_4$	40 °C	CH_2Cl_2	3	12:39:49	82
7[b]	$Rh_2(esp)_2$	40 °C	CH_2Cl_2	3	20:39:41	87
8[c]	$Cu(OTf)_2$	rt	CH_2Cl_2	12	−:−:100	70
9[c]	$Cu(hfacac)_2$	rt	CH_2Cl_2	12	9:−:91	88
10[c]	$AgBF_4$	rt	CH_2Cl_2	12	−:−:100	40
11[c]	$CuPF_6$	rt	CH_2Cl_2	12	−:−:100	86

[a]Reactions were performed with 0.1 mmol of **3a**. [b]1 mol % Rh_2L_n was used as the catalyst. [c]5 mol % catalyst was used. [d]**5a** was obtained as the *E* isomer exclusively. [e]Ratios were determined by ^1H NMR analysis of the reaction mixtures. [f]Combined yields of **4a**−**6a**.

migration (entries 8−11) compared with the dirhodium complexes. Thus, catalysts derived from different metals (Rh and Cu or Ag) direct competitive 1,2-C→C and -N→C migration pathways with high selectivities, and the 1,2-C→C migration product **4a** or the 1,2-N→C migration product **6a** could be obtained in high yield under catalysis of $Rh_2(cap)_4$ or $CuPF_6$, respectively. The 1,2-C→C and -O→C migrations appear to be linked, but highly selective catalyst-directed 1,2-O→C migration could not be achieved with **3a**.

The influence of R^1 on the selective 1,2-C→C migration catalyzed by $Rh_2(cap)_4$ and the 1,2-N→C migration catalyzed by $CuPF_6$ was investigated next (Table 3). Reactions performed

Table 3. Selective 1,2-C→C and -N→C Migrations of 3 Catalyzed by $Rh_2(cap)_4$ and $CuPF_6$, Respectively



		$Rh_2(cap)_4$[b]			$CuPF_6$[e]	
3[a]	R^1	4	4:5[c]	yield (%)[d]	6	yield (%)[f]
3a	Ph	**4a**	85:15	85	**6a**	86
3b	4-MeC_6H_4	**4b**	89:11	81	**6b**	85
3c	4-ClC_6H_4	**4c**	88:12	83	**6c**	80
3d	2-$MeOC_6H_4$	**4d**	81:19	79	**6d**	86
3e	4-$MeOC_6H_4$	**4e**	88:12	86	**6e**	78
3f	cyclohexyl	**4f**	87:13	88	**6f**	77
3g	(*E*)-Ph−CH═CH	**4g**	86:14	85	**6g**	84

[a]Reactions were performed with 0.1 mmol of **3**. [b]Reactions were performed with 1 mol % $Rh_2(cap)_4$ in $ClCH_2CH_2Cl$ at 80 °C for 3 h. [c]Determined by ^1H NMR analysis of the crude reaction mixtures. [d]Combined yields of **4** and **5**. [e]Reactions were performed with 5 mol % $CuPF_6$ in CH_2Cl_2 for 12 h at room temperature. [f]Isolated yields of **6**.

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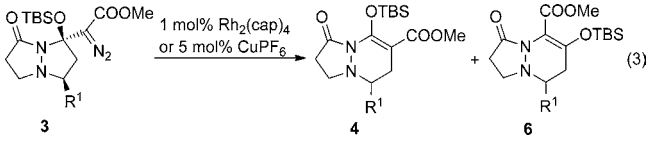
with $CuPF_6$ as the catalyst uniformly afforded the 1,2-N→C migration product, and $Rh_2(cap)_4$ was found to promote the 1,2-C→C migration process with high selectivities but without a significant dependence on R^1.

In an effort to achieve 1,2-C→C, 1,2-O→C, and 1,2-N→C migrations selectively with different catalysts, **3h**, which has an additional phenyl group on the pyrazolidinone ring, was subjected to the same series of catalytic reactions (Table 4).

Table 4. Catalyst Screening with 3h for Selective 1,2-C→C, -O→C, and -N→C Migrations



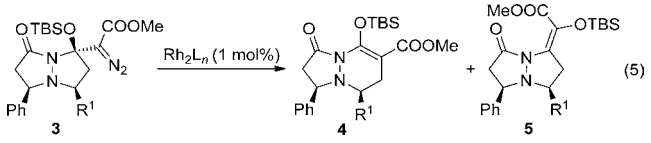
entry[a]	catalyst	solvent	time (h)	4h:5h[d]:6h[e]	yield (%)[f]
1[b]	$Rh_2(OAc)_4$	CH_2Cl_2	3	60:40:–	91
2[b]	$Rh_2(Oct)_4$	CH_2Cl_2	3	43:57:–	88
3[b]	$Rh_2(OBz)_4$	CH_2Cl_2	3	25:75:–	82
4[b]	$Rh_2(piv)_4$	CH_2Cl_2	3	12:88:–	74
5[b]	$Rh_2(esp)_2$	CH_2Cl_2	3	15:85:–	88
6[b]	$Rh_2(cap)_4$	$(CH_2Cl)_2$	1	91:9:–	86
7[b]	$Rh_2(tfa)_4$	CH_2Cl_2	3	69:31:–	81
8[b]	$Rh_2(pfb)_4$	CH_2Cl_2	3	64:36:–	79
9[c]	$CuPF_6$	CH_2Cl_2	12	–:–:100	72

[a]Reactions were performed with 0.1 mmol of **3h**. [b]Reaction was performed with 1 mol % Rh_2L_n as the catalyst. [c]Reaction was performed with 5.0 mol % $CuPF_6$ as the catalyst. [d]**5h** was obtained as the *E* isomer exclusively. [e]Ratios were determined by ^1H NMR analysis of the crude reaction mixtures. [f]Combined yields of **4h**–**6h**.

With 1 mol % $Rh_2(OAc)_4$, the formation of the 1,2-C→C migration product **4h** and the stereoselective 1,2-O→C migration product **5h** occurred without evidence for the formation of the 1,2-N→C migration product **6h** (entry 1). Once again, $Rh_2(cap)_4$ selected the 1,2-C→C migration pathway (entry 6), and $CuPF_6$ effected exclusive 1,2-N→C migration (entry 9). Consistent with entries 6 and 7 but more dramatic, increasing the steric size of the ligand by using $Rh_2(piv)_4$ (entry 4) significantly enhanced the reaction selectivity toward the formation of the 1,2-O→C migration product **5h**, and this outcome was mirrored by the use of $Rh_2(esp)_2$ (entry 5) in higher overall yield. Hence, with a simple change in the ligand attached to the dirhodium centers, the competing 1,2-C→C or 1,2-O→C migration could be made dominant through catalysis by $Rh_2(esp)_2$ [or $Rh_2(piv)_4$] or $Rh_2(cap)_4$, respectively; the 1,2-N→C migration product **6h**, which was not detected in reactions catalyzed by dirhodium complexes, was the sole migration outcome under $CuPF_6$ catalysis. In addition, as shown in Table 5, these reactions exhibited the same selectivities irrespective of the electronic nature of the substituents on the phenyl ring of R^1 and even when cyclohexyl was used in place of an aryl group.

The 1,2-C→C migration (to form **4**) and the 1,2-O→C migration (to form **5**) are linked in dirhodium-catalyzed reactions, and the causes for selectivity may be attributed to steric [e.g., results with $Rh_2(piv)_4$ and $Rh_2(esp)_2$] and electronic [results with $Rh_2(cap)_4$] factors. However, the unexpected 1,2-N→C migration from **3** to form **6**,[15] which is formally an amide nitrogen migration, stands out as exceptionally favorable when copper rather than dirhodium catalysts are

Table 5. Substrate Scope for Ligand-Induced Divergent 1,2-C→C and -O→C Migrations

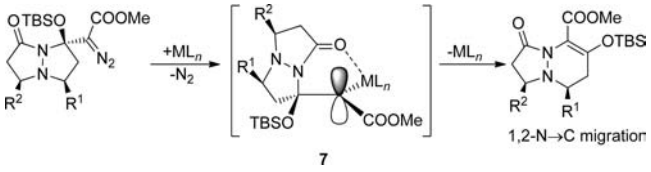


		$Rh_2(cap)_4$[b]			$Rh_2(esp)_2$[c]		
3[a]	R^1	4	4:5[d]	yield (%)[e]	5[f]	4:5[d]	yield (%)[e]
3h	Ph	**4h**	91:9	91	**5h**	15:85	88
3i	4-$NO_2C_6H_4$	**4i**	97:3	90	**5i**	16:84	86
3j	4-$MeOC_6H_4$	**4j**	96:4	92	**5j**	17:83	85
3k	4-BrC_6H_4	**4k**	93:7	93	**5k**	10:90	85
3l	3-BrC_6H_4	**4l**	88:12	91	**5l**	14:86	82
3m	cyclohexyl	**4m**	75:25	86	**5m**	15:85	92

[a]Reactions were performed with 0.1 mmol of **3** with 1 mol % Rh_2L_n as the catalyst. [b]Reactions were performed in $ClCH_2CH_2Cl$ at 80 °C for 1 h. [c]Reactions were performed in CH_2Cl_2 at room temperature for 3 h. [d]Determined by ^1H NMR analysis of the reaction mixtures. [e]Combined yields of **4** and **5**. [f]Obtained as the *E* isomer exclusively.

employed. This heightened selectivity for **6** may be due to coordination of the copper carbene intermediate[16] with the carbonyl oxygen of the pyrazolidinone ring (**7** in Scheme 2), a

Scheme 2. Directing Effect in Cu-Catalyzed 1,2-N→C Migration



complexation that would not be expected with the coordinatively saturated dirhodium complexes.[17] Consequently, the overall 1,2-N→C migration is facilitated by transition-metal catalysts with open coordination sites.

In summary, we have discovered catalyst-controlled highly selective 1,2-C→C, -O→C, and -N→C migrations of *β*-methylene-*β*-silyloxy-*β*-amido-*α*-diazoacetates. These rearrangement reactions produce a variety of highly functionalized dinitrogen-fused heterocyclic compounds. Further studies of these intriguing migrations are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, optimization of reaction conditions, characterization data, and crystallographic data for **3a**, **4h**, **5k**, and **6c** (CIF). 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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