Simultaneous and Stereoselective Construction of Planar and Axial Centers of Chirality

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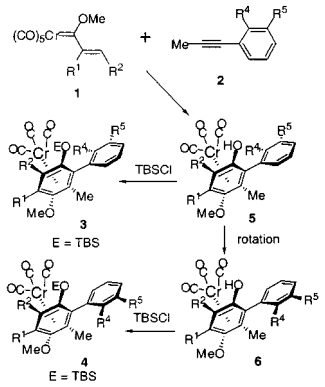
Atropisomerism resulting from hindered rotation about single bonds can lead to molecules with centers of axial chirality and are widely used in asymmetric catalytic synthesis.[1] Molecules containing planar centers of chirality have also been used as chiral ligands, particularly those containing η^6-benzene and η^5-cyclopentadienyl complexes.[2] To our knowledge, there are no known synthetic methods that produce both types of chiral centers in a single step. The reaction of Fischer carbene complexes with aryl alkynes has the potential for the synthesis of molecules that contained both planar and axial centers of chirality (Scheme 1). We report here the first examples of the simultaneous synthesis of centers of planar and axial chirality and furthermore that this can be accomplished with high levels of relative diastereoselection.

Aside from the issue of the stereoselectivity of the benzannulation of carbene complexes with aryl alkynes of the type **2**, we were concerned about the facility of the reaction in general since the benzannulation of hindered alkynes is known to lead to the formation of several different types of side products including indenes and cyclobutanones.[3] We were thus delighted to see that the reaction of complex **1a** with alkyne **2a** gives good yields of the arene chromium tricarbonyl complexed product after trapping of the phenol function with *tert*-butyldimethylsilyl chloride (Table 1, entries 1 and 2).[4] It was quite remarkable to find that either diastereomer **3a** or **4a** could be obtained selectively, depending on the reaction conditions. If *tert*-butyldimethylsilyl chloride and Hunig's base are added at the beginning of the reaction (Method A, one pot), a 89:11 mixture of isomers is obtained. On the other hand, if the silylation is performed in a separate step after the benzannulation reaction is complete (Method B, seq), then a 97:3 selectivity is obtained for the other diastereomer. Similar results are seen for the reaction of complex **1a** with the alkynes **2b**, **2c**, and **2d** as indicated by the data in Table 1. For the alkynes **2c** and **2d** bearing larger groups in the ortho position, the temperature needs to be increased 120 °C to effect complete conversion to the thermodynamic products **4c** and **4d** (entries 6 and 8).

Scheme 1



To explain the different stereochemical outcomes of this reaction, it was reasoned that isomerization about the axial center may be occurring prior to protection of the phenol with the *tert*-butyldimethylsilyl group. Clearly the hydroxyl group would present less of a steric encumbrance to rotation about the bond than a *tert*-butyldimethylsilyloxy group. Thus, under the conditions of Method B, the phenol function remains unprotected until the completion of the reaction. This provides time for isomerization to the more stable thermodynamic product which is expected to be the phenol chromium tricarbonyl complex **6** with the ortho substituent of the alkyne anti to the chromium tricarbonyl group to minimize steric interactions. If this were true, the kinetic product must be the phenol complex **5** with the ortho substituent of the alkyne syn to the metal center. Only the reaction of the trans-*tert*-butylvinyl complex **1d** gives a stable phenol chromium tricarbonyl complex. These reactions were performed at 50 °C in the absence of a trapping agent to give a 65:35 mixture in favor of **5n**, but at 120 °C exclusive formation of **6n** is observed.

That the thermodynamic product is the anti product **4** was confirmed in the reaction of the cyclohexenyl carbene complex **1c** with alkyne **2a**. In this case, the same isomer predominated under both the one-pot and the sequential conditions. This stereoisomer was formed in a 21:79 ratio under the one-pot conditions at 50 °C (entry 11). Although this mixture of compounds was slow to isomerize at 50 °C under the conditions of Method B, it did completely undergo conversion to a single atropisomer (= 1:99) under Method B when the reaction time was extended to 48 h for the first step (entry 13 vs 12). Alternatively, complete conversion to **4f** could be effected by raising the temperature to 80 °C (entry 15). The stereochemistry of the thermodynamic product from this reaction was determined to be the anti isomer **4f** by X-ray diffraction analysis on a single crystal. The assignment of the thermodynamic isomers obtained from the reaction of the cyclohexenyl complex **1c** with alkynes **2c**, **2e**, **2d**, and **2k** were assigned as the anti isomers **4** in analogy with **4f** and by ^{1}H NMR correlation with **4f**. For all of these alkynes, the reaction products could be completely isomerized to the anti isomer by performing the reaction at 120 °C except for the smaller ortho methoxyl complex which only required 50 °C for complete conversion. This includes the very hindered *tert*-butyl complex **3i** which was formed as a slightly preferred kinetic product having the syn stereochemistry which was determined by X-ray diffraction. The reactions of the alkynes **2g** and **2h** with complex **1c** gave a single diastereomer with the one-pot conditions of Method A at 50 °C, and thus it was not possible to determine if the observed isomer is also the thermodynamic isomer. Therefore, the assignment of the stereochemistry of **4l** and **4m** was determined by X-ray diffraction analysis of a single crystal.

While high selectivities could be obtained for the thermodynamic anti product from the reactions of all of the carbene

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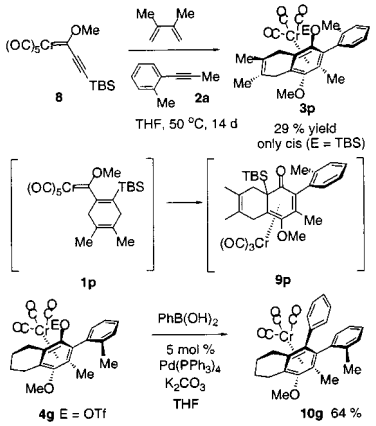
Table 1. Stereoselective Benzannulation of Carbene Complexes **1** with Aryl Alkynes

entry	complex	R^1	R^2	alkyne	R^4	R^5	method[b]	time (h)[c]	temp (°C)	product series[d]	yield **3**+**4**[e]	ratio **3**:**4**	yield free arene **7**
1	**1a**	H	Me	**2a**	Me	H	A: 1 pot	24	50	a	63	89:11	4
2	**1a**	H	Me	**2a**	Me	H	B: seq	24, 24	80	a	62	3:97	2
3	**1a**	H	Me	**2b**	CH_2OTBS	H	A: 1 pot	24	50	b	53	>99:1	8
4	**1a**	H	Me	**2b**	CH_2OTBS	H	B: seq	48, 24	50	b	58	6:94	0
5	**1a**	H	Me	**2c**	*i*-Pr	H	A: 1 pot	12	50	c	56	94:6	8
6	**1a**	H	Me	**2c**	*i*-Pr	H	B: seq	24, 24	120	c	33	≤1:99	16
7	**1a**	H	Me	**2d**	-CH=CHCH=CH-		A: 1 pot	24	50	d	57	89:11	1
8	**1a**	H	Me	**2d**	-CH=CHCH=CH-		B: seq	24, 24	120	d	47	≤1:99	16
9	**1b**	Me	H	**2a**	Me	H	A: 1 pot	3	50	e	61	22:78	3
10	**1b**	Me	H	**2a**	Me	H	B: seq	24, 24	120	e	63	2:98	5
11	**1c**	$-(CH_2)_4-$		**2a**	Me	H	A: 1 pot	24	50	f	77	21:79	0
12	**1c**	$-(CH_2)_4-$		**2a**	Me	H	B: seq	24, 24	50	f	75	14:86	0
13	**1c**	$-(CH_2)_4-$		**2a**	Me	H	B: seq	48, 24	50	f	66	≤1:99	1
14	**1c**	$-(CH_2)_4-$		**2a**	Me	H	A: 1 pot	24	80	f	66	23:77	0
15	**1c**	$-(CH_2)_4-$		**2a**	Me	H	B: seq	24, 24	80	f	74	2:98	5
16	**1c**	$-(CH_2)_4-$		**2a**	Me	H	C: seq	24, 24	80	g	86[f]	≤1:99	0
17	**1c**	$-(CH_2)_4-$		**2c**	*i*-Pr	H	A: 1 pot	24	50	h	70	35:65	1
18	**1c**	$-(CH_2)_4-$		**2c**	*i*-Pr	H	B: seq	24, 24	120	h	64	1:99	5
19	**1c**	$-(CH_2)_4-$		**2e**	*t*-Bu	H	A: 1 pot	24	50	i	75	57:43	2
20	**1c**	$-(CH_2)_4-$		**2e**	*t*-Bu	H	B: seq	24, 24	120	i	67	<1:99	0
21	**1c**	$-(CH_2)_4-$		**2d**	-CH=CHCH=CH-		A: 1 pot	24	50	j	78	40:60	0
22	**1c**	$-(CH_2)_4-$		**2d**	-CH=CHCH=CH-		B: seq	24, 24	120	j	59	<1:99	7
23	**1c**	$-(CH_2)_4-$		**2f**	OMe	H	A: 1 pot	24	50	k	91	28:72	1
24	**1c**	$-(CH_2)_4-$		**2f**	OMe	H	B: seq	24, 24	50	k	73	2:98	2
25	**1c**	$-(CH_2)_4-$		**2g**	OTBS	H	A: 1 pot	24	50	l	70	<1:99	2
26	**1c**	$-(CH_2)_4-$		**2h**	CO_2Me	H	A: 1 pot	24	50	m	74	<2:98	1
27	**1d**	H	*t*-Bu	**2a**	Me	H	D: none	24	50	n	69[g]	65:35	0
28	**1d**	H	*t*-Bu	**2a**	Me	H	D: none	24	120	n	60[g]	≤1:99	12
29	**1e**	H	TBS	**2a**	Me	H	D: none	24	50	o	73	≤3:97	0

[a] Unless otherwise specified, all reactions were run in toluene under an argon atmosphere with 1.5 equiv of **1** and at 0.25 M in **2** and protected from room light. [b] Method A: Reaction performed in the presence of 3 equiv of TBSCl and 5 equiv of Et-Pr_2N. Method B: Reaction performed for indicated time and then in a subsequent step 3 equiv of TBSCl and 5 equiv of Eti-Pr_2N was added and the silylation performed at the same temp and time. Both steps were performed at the indicated temperature. Method C: same as B except that triflic anhydride substituted for TBSCl. Method D: Reaction performed in the absence of TBSCl and Eti-Pr_2N. [c] Time for second step indicated second. [d] E = TBS except for entries 16 (E = Tf) and 27 and 28 (E = H). [e] Determined by ^{1}H NMR on isolated mixture of **3**, **4**, and metal free biaryl **7** derived from **3** or **4**. [f] Product **4g** isolated as triflate (E = SO_2CF_3). [g] Product isolated as phenol chromium tricarbonyl complex **5** or **6**.

Scheme 2



complexes and all of the alkynes, it was possible to obtain high selectivity for the kinetic syn product only from the reactions of the trans-propenyl complex. This could be the result of more extensive isomerization of the syn intermediate **5** to **6** for the cyclohexenyl complex **1c** than for the trans-propenyl complex **1a**. A test for this possibility was carried out by the reaction of the alkynyl complex **8** with 2,3-dimethylbutadiene in the presence of the alkyne **2a** (Scheme 2). The expected domino reaction sequence includes the Diels−Alder reaction to produce the cycloadduct carbene complex **1p** and then subsequent benzannulation reaction with the alkyne to produce **3p** with the 1,3-migration of silicon to oxygen as the final step.[4,5] Since a free phenol complex is never an intermediate in this reaction, the diastereoselection in this reaction should be indicative of the kinetic stereoselection in these reactions. In fact, this reaction produces the biaryl complex **3p** as a single diastereomer which was shown to be the syn isomer by X-ray diffraction of a single crystal. This result is suggestive that the syn isomer is formed in high selectivity from the reaction of the cyclohexenyl complex, however, the result in entry 29 of Table 1 reveals that the kinetic selectivity is substrate dependent. The reaction of complex **1e** should also proceed to give the biaryl complex **4o** without the intermediacy of a phenol complex, and yet this complex produces the anti complex (**4o**, R^1, R^2, R^5 = H, R^4 = Me) with high selectivity as determined by ^{1}H NMR correlation with compounds **3** and **4** in Table 1.

Finally it was shown that the chromium biphenol complexes could be trapped with triflic anhydride as illustrated by the isolation of the triflate complex **4g** in 86% yield and was shown to be exclusively the anti diastereomer by X-ray diffraction (entry 16). The synthetic utility of these triflate complexes is illustrated by the Suzuki coupling of **4g** with phenyl boronic acid to give the arene complex **10g** where the presence of the chromium tricarbonyl group undoubtedly aids in the coupling at this very hindered center[6] (Scheme 2).

We will report in the future on the utility of this diastereoselective benzannulation for the synthesis of molecules containing both axial and planar centers of chirality, on studies directed to determining the origin of the diastereoselection, and on efforts to develop asymmetric versions of this reaction.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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