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Formation of Vinyl-, Vinylhalide- or Acyl-Substituted Quaternary Carbon Stereogenic Centers through NHC–Cu-Catalyzed Enantioselective Conjugate Additions of Si-Containing Vinylaluminums to β -Substituted Cyclic Enones

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Abstract

A catalytic method for enantioselective conjugate addition (ECA) of Si-containing vinylaluminum reagents to β-substituted cyclopentenones and cyclohexenones is described. Reactions are promoted by 1.0–5.0 mol % of a bidentate NHC–Cu complex, which is prepared from air stable $CuCl_2 \cdot 2H_2O$ and used in situ, and typically proceed to completion within 15–20 minutes. The requisite vinylmetals are generated efficiently by a site-selective hydroalumination of an alkyne with dibal–H. The desired products, containing a quaternary carbon stereogenic center, are obtained in 48–95% yield after purification and in 89:11 to >98:2 enantiomer ratio (er). The vinylsilane moiety within the products can be functionalized to afford acyl, vinyliodide or desilylated alkenes in 67% to >98% yield and with >90% retention of the alkene's stereochemical identity. The utility of the catalytic process is illustrated in the context of a concise enantioselective synthesis of riccardiphenol B.

Catalytic enantioselective conjugate additions of easily accessible C-based nucleophiles to unsaturated carbonyls faciliates the synthesis of a range of enantiomerically enriched biologically active molecules and are therefore of significant value.[1] Nevertheless, in spite of recent advances,[2] notable shortcomings persist in this area, particularly in the context of reactions furnishing quaternary carbon stereogenic centers.[3] One deficiency relates to the paucity of protocols for catalytic conjugate additions of vinyl units.[4] A report regarding Cu–phosphine-catalyzed enantioselective conjugate addition (ECA) reactions of vinylaluminums with β-substituted cyclic enones has appeared; however, substrate and reagent scope is narrow and the preparation of the requisite vinylmetals via vinylhalides can be limiting (details below).[5] We set out to examine whether Cu complexes of N-heterocyclic carbenes (NHCs) can effect ECA of vinylmetals to generate quaternary carbon stereogenic centers.[6] In this context, use of Si-substituted vinylmetals would be attractive (Scheme 1) for several reasons. First, efficient and stereoselective hydroaluminations of silylacetylenes with inexpensive diisobutyaluminum hydride (dibal–H) afford the requisite vinylaluminums.[6] Thus, the need for stereoselective synthesis of vinylhalides, only a few of which can be purchased and whose preparation often requires strongly acidic conditions,[7] would not be necessary. Second, in instances where the vinylmetal is a small molecule, the impracticality of isolation or purification of volatile alkynes or vinylhalides can be avoided. Third, and perhaps most importantly, as illustrated in Scheme 1, efficient synthesis of a variety of

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enantiomerically enriched products that cannot be directly prepared or, at least, easily synthesized by a catalytic process would become feasible due to the presence of the vinylsilane.

Herein, we report a method for enantioselective conjugate addition of 1-Si-substituted vinylaluminum reagents to five- and six-membered β-substituted cyclic ketones. Reactions are catalyzed by a chiral bidentate NHC–Cu complex derived from air stable and commercially available $CuCl_2 \cdot 2H_2O$ and afford the desired products in up to 95% yield and >98:2 enantiomeric ratio (er). The resulting enantiomerically enriched vinylsilanes can be protodesilylated, converted to the corresponding vinyl halides, or oxidized to β-acyl-substituted enones in >66% yield. The utility of the NHC–Cu-catalyzed reaction is illustrated through a concise total synthesis[8] of natural product riccardiphenol B.[9]

From the outset, we appreciated that efficiency of the aforementioned processes would hinge on identification of a chiral catalyst that accomplishes the demanding task of forming the highly congested C–C bond. We were aware that the attendant steric congestion, as well as stabilization of electron density at the Si-bearing carbon might result in diminution of vinylaluminum nucleophilicity to decelerate the vinyl addition process, allowing alternative pathways to become competitive. In the context of Cu-catalyzed allylic substitutions, we had observed that Si-substituted vinylaluminums, although effective in reactions that furnish tertiary C–C bonds, give rise to inefficient and non-selective processes when quaternary carbon stereogenic centers are to be generated.[10] Such concerns were validated in the present studies by the observation that with the NHC–Cu derived from dimeric Ag complex **1** (easily accessed from the imidazolinium salt and Ag_2O)[11] and $CuCl_2 \cdot 2H_2O$, ECA with β-methylcyclopentenone and vinylsilane **6** delivers 20% of the desired **7a** (10:90 er)[12] along with 15% of allylic alcohol **9** (entry 1, Table 1). Reaction efficiency (>98% vs 35% conv) and the preference for transfer of the vinyl unit (85% vs 20%) improve significantly with the sulfonate-bridged complex derived from **2**[13] to afford the β-vinyl ketone in 80:20 er (entry 2, Table 1). Similar efficiency is furnished by the Cu-complex accessed through **3a** (entry 3), but enantioselectivity is increased to 90:10 er. Further improvement in efficiency (<2% unidentified products) and selectivity (95% **7a** in 93:7 er; 5% **8**[14]) are attained with **3b**, which contains a larger NAr group (entry 4, Table 1). Somewhat surprisingly, NHC–Cu complex derived from **3c**, where the size of the NAr is increased further, proves to be substantially less effective (entry 5). As the data in entries 6–7 of Table 1 indicate, ECA with monodentate NHC–Cu complexes, are inefficient, although in one case reasonably selective (17:83 er in entry 6).[15] The relative ineffectiveness of complexes derived from **4** and **5** is in contrast to ECA processes that generate C–B[16] or C–Si[17] bonds, where monodentate NHC–Cu catalysts emerge as optimal. The above findings thus illustrate that, in contrast to allylic substitutions with trisubstituted alkenes,[10] ECA to cyclic enones with Si-substituted vinylaluminums proceed efficiently and with high enantioselectivity in the presence of sulfonate-based NHC–Cu complexes. The precise reason for such reactivity and selectivity difference is unclear, but might be partly due to higher electrophilicity of unsaturated carbonyls (vs allylic phosphates).

β-Alkyl-substituted cyclopentenones and a range of alkyl- as well as aryl-substituted 1-trimethylsilyl-vinylaluminums (entries 1–6, Table 2) undergo ECA efficiently (>98% conv in 20 min) and with high enantioselectivity (92.5:7.5–95.5:4.5 er). Reactions with β-substituted cyclohexenones proceed to afford the desired products in up to 98.5:1.5 er (entries 7–12, Table 2). Although there is 4–33% *i*-Bu addition in transformations shown in Table 2, <2% adventitious 1,2-reduction (cf. **9**, Table 1) is detected and pure β-vinyl cycloalkanones are isolated in 50–95% yield. Two additional points regarding the reactions in Table 2 are noteworthy: (1) Cyclopentenones, a particularly challenging substrate class for ECA reactions,[18] generally react more efficiently than cyclohexenones (90:10–95:5 vs

67:33–96:4 vinyl:*i*-Bu addition). (2) Cu-catalyzed ECA can be performed with lower catalyst loading than used in the studies summarized in Table 2. As an example, with 0.5 mol % **3b** and 1.0 mol % CuCl$_2$•2H$_2$O, the processes in entries 1 and 8 of Table 2 proceed to >98% conv in 1.5 h (22 °C) to afford products with the same level of enantioselectivity and in 68% and 85% yield, respectively.

Catalytic additions to cycloheptenones are inefficient (20–40% conv to the vinyl addition product). Relatively large β substituent lead to diminished reaction rates, as demonstrated by the transformation of enone **11** (Scheme 2), affording **12** in 48% yield after purification and 89:11 er. Efficient and highly enantioselective synthesis of **13** (Scheme 2), bearing a *gem*-dimethyl group at its C2' position, demonstrates that improved selectivity can be achieved with sterically demanding ketones (>98:2 er vs 93:7 er in entry 1, Table 2). As the preparation of **14–15** illustrates, vinylaluminum reagents bearing a more hindered silyl unit (*t*-BuMe$_2$Si vs SiMe$_3$) can be used to access β-vinyl carbonyls efficiently and in high er. Protodesilylation of **14** or **15** (see below for procedure) will generate β-vinyl products that cannot be as easily accessed through the use of the volatile vinyl halide(metal- halogen exchange/reaction with aluminum-halide) or hydroalumination of acetylene.

The transformations depicted in Scheme 3 highlight the utility of the Si-containing ECA products. Through a two-step procedure that includes site-selective epoxidation of the vinylsilane followed by a rearrangement induced by a mild acid,[19] enone **16** – the product of a hitherto unknown enantioselective acyl anion conjugate addition[20] – is obtained in 67% yield. Subjection of **7b** to *N*-iodosuccinimide[21] delivers enantiomerically enriched vinyl iodide **17**, which can be used in catalytic cross-coupling,[22] in 91% yield as a 91:9 *Z:E* mixture. Similar conversion to **18** proceeds in quantitative yield and without detectable loss of alkene stereochemistry (>98% *E*). Protodesilylation with trifluoroacetic acid is highly effective as well: synthesis of **19–20** in 76% and >98% yield, respectively, are representative.[23]

The utility of the method is demonstrated through enantioselective synthesis of riccardiphenol B (Scheme 4).[24] NHC–Cu-catalyzed reaction of commercially available β-methylcyclohexenone with complex **3b** and vinylaluminum **21**, conveniently and selectively prepared by hydroalumination of the corresponding enyne, followed by treatment with Ac$_2$O furnishes enol acetate **22** in 67% overall yield and 98.5:1.5 er. Generation of the corresponding Li-enolate by subjection of **22** to *n*-BuLi and addition of excess *o*-quinone methide **23**, prepared and used in situ,[25] leads to the formation of the derived α-benzyl adduct (>98:2 dr).[26] Subsequent ketone alkylation with MeLi affords tertiary carbinol **24** in 70% overall yield. Formation of the tetrasubstituted olefin with SOCl$_2$ and protodesilylation delivers the target molecule.

Development of additional catalytic enantioselective C–C bond forming processes that are promoted by NHC-based chiral catalysts and involve vinylic organometallic reagents as nucleophiles are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(12). For determination of absolute stereochemistry of the ECA products, see the Supporting Information.

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(14). The *i*-Bu addition product (**8**) is generated through an NHC–Cu-catalyzed process in 89:11 er. See [ref 2h].

(15). The opposite sense of absolute stereochemistry observed with sulfonate-containing Cu complexes derived from **2** and **3a–c** (entries 2–5, Table 1), vs those obtained through phenoxy-based **1** (entry 1) or monodentate **4** (entry 6), might be due to their unique stereochemical characteristics.

Structural studies indicate that, unlike the bridging aryloxide in **1** or monodentate carbenes such as those obtained via **4** and **5**, the sulfonate in such chiral Cu complexes is oriented *syn* to the neighboring Ph group of the NHC backbone. See: Lee Y, Li B, Hoveyda AH. J. Am. Chem. Soc. 2009; 131:11625. [PubMed: 19630406]

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(23). Preliminary studies indicate that, under the same conditions, NHC–Cu-catalyzed addition of non-silyl-containing β-vinylaluminum reagents proceeds with equal efficiency but lower enantioselectivity (e.g., **19** in 65:35 er) but with the same sense of absolute stereochemistry. Investigations regarding identification of catalysts and conditions that promote such processes with high efficiency and enantioselectivity are in progress and will be reported in due course.

(24). Riccardiphenol B has previously been synthesized by a 12-step sequence through utilization of a chiral auxiliary-based process. See: (a) Tori M, Hamaguchi T, Sagawa K, Sono M, Asakawa Y. J. Org. Chem. 1996; 61:5362.. For preparation of analogs in the racemic form, see: (b) Kumar SK, Amador M, Hidalgo M, Bhat SV, Khan SR. Bioorg. Med. Chem. 2005; 13:2873. [PubMed: 15781397]

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(26). Treatment of the Li-enolate derived from **22** with the appropriately substituted benzyl bromide leads to <2% of the desired alkylation product. In contrast, when benzyl bromide is used, the desired product is obtained in 74% yield (>20:1 dr). The above findings suggest that subtle structural alterations of the electrophile can inhibit reaction of the sterically congested enolate. The stereochemical identity of the alkylation product (>98% dr) is projected based on steric factors and has not been rigorously determined.
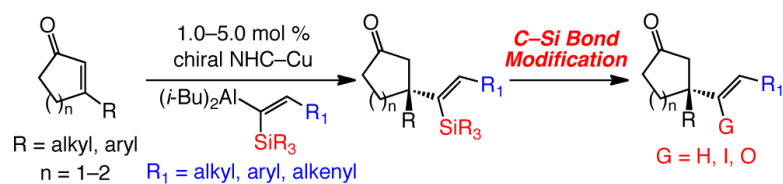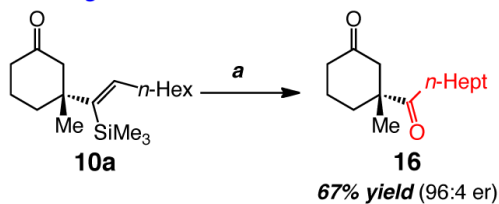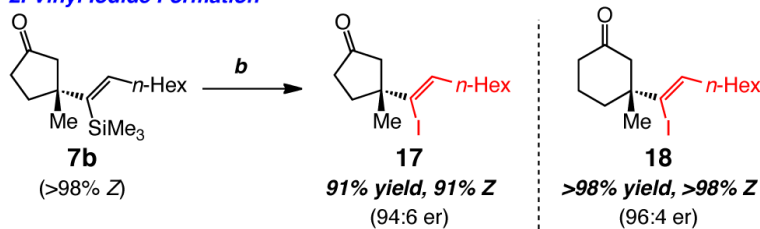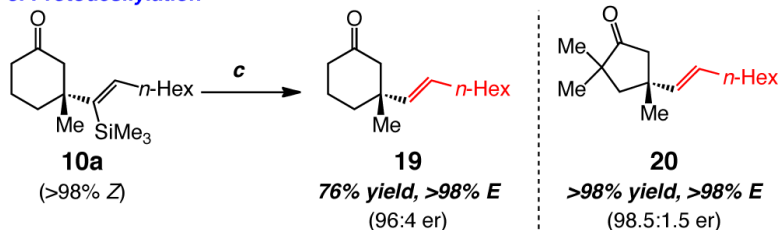
Scheme 1.
Versatility of Catalytic Conjuagte Additions with Si-Substituted Vinylaluminum Reagents
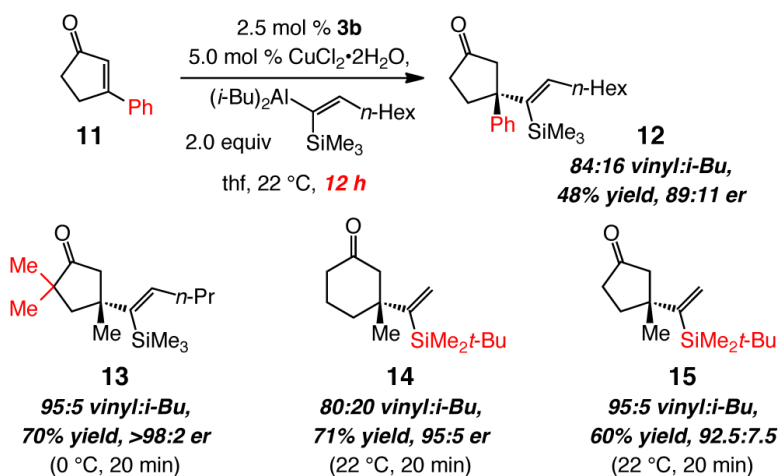
Scheme 2.
More Variations in Vinylaluminum Reagent and Substrate[a]

[a]Reactions performed under conditions used in Table 1–2, with the noted specifications; conv. (>98% in all cases), yields and selectivity values determined as in Table 1–2. Percent vinyl addition is relative to the *i*-Bu byproduct and not an absolute value.

Scheme 3.
Utility of the Enantiomerically Enriched Vinylsilanes
Conditions: (a) 1. 1.5 equiv *m*-chloroperbenzoic acid, CH$_2$Cl$_2$, 0 °C, 3 h; 96%. 2. HCO$_2$H, 100 °C, 1 h; 70%. (b) 2.6 equiv *N*-iodosuccinimide, MeCN, 0–22 °C, 12 h. (c) F$_3$CCO$_2$H, CHCl$_3$, 22 °C, 6 h.
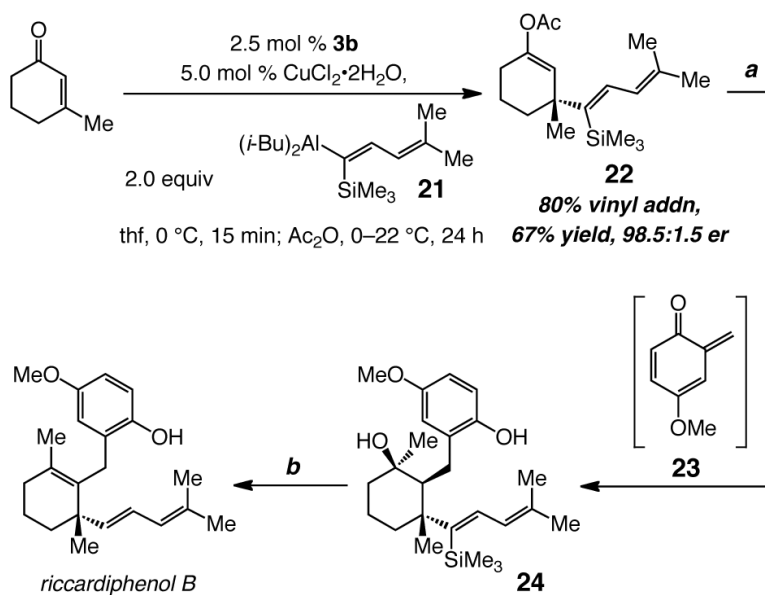
Scheme 4.
Application to Enantioselective Synthesis of Riccardiphenol B
Conditions: (a) 1. 2.5 equiv *n*-BuLi, thf, 0–22 °C, 1.5 h; 10 equiv **23**, −78–22 °C, 12 h. 2. 10 equiv MeLi, thf, 0–22 °C, 3 h; 70% overall (2 steps). (b) 1. 10 equiv SOCl$_2$, pyr, 0–22 °C; 61%. 2. 10 equiv (*n*-Bu)$_4$NF, 110 °C, 6 h; 62%.

Table 1

Initial Examination of Various Chiral NHC Complexes[a]

3a Ar = 2,4,6-(Me)₃C₆H₂ (Mes)
3b Ar = 2,6-(Et)₂C₆H₃
3c Ar = 2,6-(i-Pr)₂C₆H₃
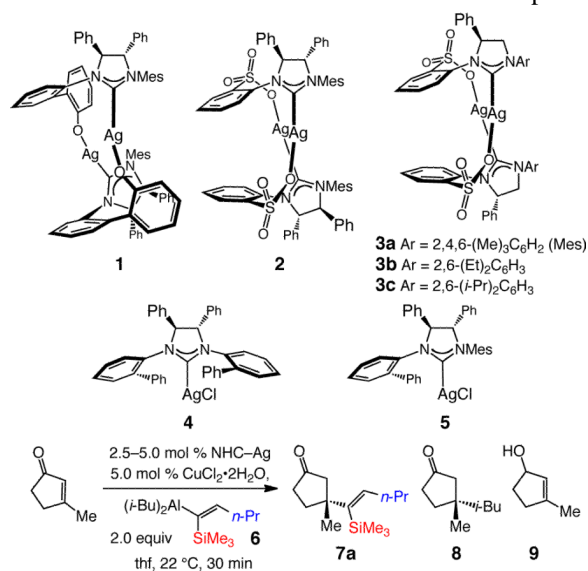
entry	NHC-Ag; mol %	conv (%)[b]	7a:8:9[b]	er (7a)[c]
1	**1**; 2.5	35	20:<2:15	10:90
2	**2**; 2.5	>98	85:<2:15	80:20
3	**3a**; 2.5	>98	86:05:09	90:10
4	**3b**; 2.5	>98	95:05:<2	93:7
5	**3c**; 2.5	70	46:21:03	52:48
6	**4**; 5.0	31	28:<2:03	17:83
7	**5**; 5.0	15	04:<2:11	nd

[a]Reactions performed under N₂ atm.

[b]Determined by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures and refers to consumption of the substrate.

[c]Determined by GLC analysis; see the Supporting Information for details.

Table 2

Cu–NHC-Catalyzed Enantioselective Conjugate Additions of Si-Substituted Vinylaluminums to β-Substituted Cyclic Enones[a]
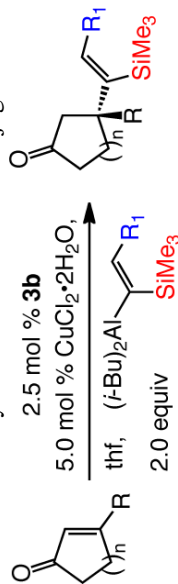
entry	substrate (R; n)		reagent (R$_1$)	temp (°C); time (min)	vinyl:i-Buaddn[b]	vinyl prod yield (%)[c]	er[d]
1	Me; 1	**7a**	n-Pr	22; 15	95:5	76	93:7
2	Me; 1	**7b**	n-Hex	22; 15	91:9	91	94:6
3	Me; 1	**7c**	(CH$_2$)$_4$O-t-Bu	0; 15	95:5	80	92.5:7.5
4	Me; 1	**7d**	Ph	22; 15	90:10	75	95:5
5	Me; 1	**7e**	p-MeOC$_6$H$_4$	22; 20	92:8	67	94:6
6	(CH$_2$)$_2$Ph; 1	**7f**	n-Hex	22; 15	95:5	95	95.5:4.5
7	Me; 2	**10a**	n-Hex	0; 20	71:29	64	96:4
8	Me; 2	**10b**	n-Pr	0; 20	85:15	85	97:3
9	Me; 2	**10c**	(CH$_2$)$_4$O-t-Bu	0; 20	96:4	85	96:4
10	Me; 2	**10d**	Ph	0; 20	67:33	50	98.5:1.5
11	Me; 2	**10e**	p-MeOC$_6$H$_4$	0; 20	78:22	66	98.5:1.5
12	4-hexenyl; 2	**10f**	n-Pr	0; 20	80:20	63	96:4

[a] Reactions performed under N$_2$ atm.

[b] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures and refers to consumption of the substrate.

[c] Yields of isolated and purified vinyl addition products.

[d] Determined by GLC analysis; see the Supporting Information for details.