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# Catalytic Enantioselective Conjugate Addition of Stereodefined Di- and Trisubstituted Alkenylaluminum Compounds to Acyclic Enones

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*Dedicated to our friend, Professor Eric N. Jacobsen, on the occasion of his sixtieth birthday.*

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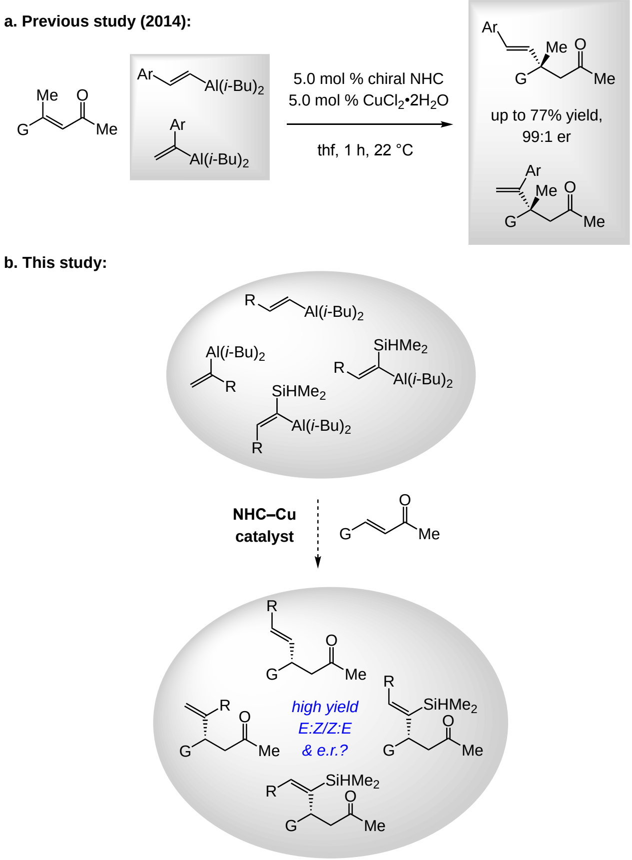
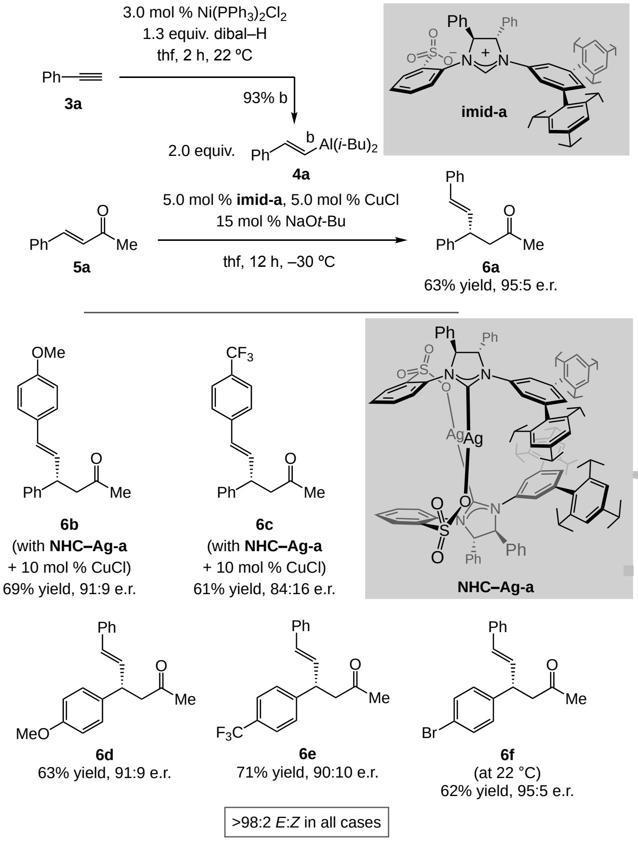
**Abstract.** Catalytic enantioselective conjugate addition (ECA) reactions with readily accessible and stereochemically defined di- and *E*-, or *Z*-trisubstituted alkenyl aluminum compounds are disclosed. Transformations are promoted by various NHC–copper catalysts (NHC = N-heterocyclic carbene), which are derived from enantiomerically pure sulfonate imidazolinium salts. The desired products were obtained in up to 89% yield and >99:1 e.r.; the alkenyl moiety was transferred with complete retention of its stereochemical identity in all instances. The scope and limitations of the approach, key mechanistic attributes, and representative functionalization are presented as well.

**Keywords:** aluminum–hydride addition; conjugate addition; Cu; N-heterocyclic carbenes; Ni

There has been considerable progress in the development of catalytic enantioselective conjugate addition (ECA) reactions in recent years, as is evident from the use of such transformations in a number of complex molecule total syntheses.[1] However, key shortcomings remain, one being the availability of transformations involving acyclic α,β-unsaturated carbonyl compounds, substrates that are conformationally less rigid (i.e., addition might occur via s-*cis* or s-*trans* conformer[2]). Furthermore, while catalytic ECA reactions that lead to incorporation of a select number of alkenyl units have been disclosed,[3–6] those that allow for the addition of a wider range of these versatile moieties are yet to be reported. In 2014 we demonstrated that α- or β-alkenyl–Al compounds through bisphosphine–Ni-catalyzed Al–H addition to terminal alkynes, may be used in efficient ECA reactions that generate a quaternary carbon stereogenic center (Scheme 1a).[7] However, reactions with a wider range of alkenyl–Al reagents (i.e., those bearing a trisubstituted olefin) or those that can generate a tertiary stereogenic carbon center are yet to be introduced. Herein, we outline the results of our investigations to address this deficiency in the state-of-the-art (Scheme 1b).



**Scheme 1.** A reported catalytic ECA method with alkenyl–Al compounds and the key goals of the present study.



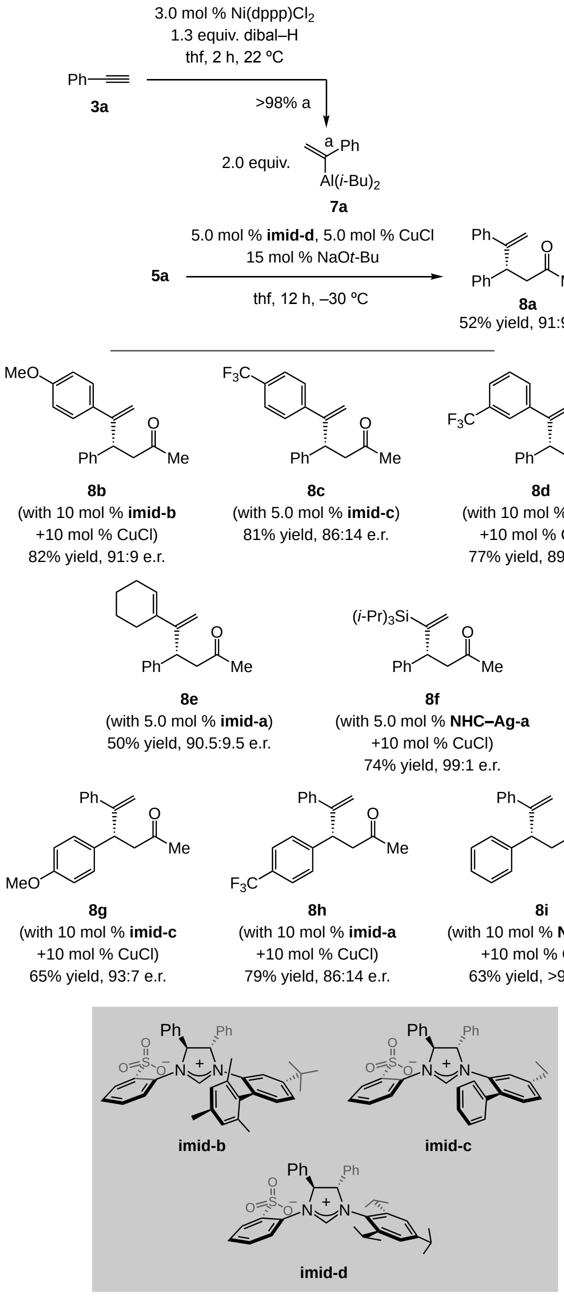
**Scheme 2.** NHC–Cu-catalyzed ECA with 1,2-disubstituted *E*-alkenyl–Al compounds. Reactions were carried out under $N_2$, and yields correspond to isolated and purified products (±5%). *E*:*Z* ratios were determined by analysis of the $^1$H NMR spectra of unpurified product mixtures (±2%). Enantiomeric ratios were determined by HPLC analysis (±1%). See the Supporting Information for details.

We began by examining the addition of a 1,2-disubstituted *E*-alkenyl–Al compound **4a** to an acyclic α,β-unsaturated ketone **5a** (Scheme 2). To identify an optimal catalyst, we investigated the reaction between **4a**, which was generated in two hours at ambient temperature through β- and *E*-selective bisphosphine–Ni-catalyzed Al–H addition to phenylacetylene (93:7 β:α, >98:2 *E*:*Z*),[8] and enone **5a**. We thus established that, in the presence of 5.0 mol % **imid-a** and CuCl in thf, after 12 h, and at –30 °C, β-alkenyl ketone **6a** may be isolated in 63% yield and 95:5 enantiomeric ratio (e.r.). Reactions with more electron-rich or electron-deficient alkyl–Al compounds proceeded with similar efficiency and enantioselectivity (**6b-c**, Scheme 2), but yields improved with **NHC–Ag-a** as the catalyst precursor at higher catalyst loading (10 vs. with 5.0 mol % **imid-a**: 55% yield, 91:91:0 e.r. and 48% yield, 84:16 e.r. for **6b** and **6c**, respectively). The precise reason for this difference has not be rigorously determined; however, considering the fact that NHC–Ag complexes are exceptionally efficient carbene transfer agents, it appears that substrate or product decomposition was caused by uncoordinated Cu(I) complexes. In contrast, ECA involving enones bearing electron-rich or electron-deficient aryl moieties were carried out under the same conditions as were used with **5a**, allowing us to isolate **6d-f** in up to 71% yield and 95:5 e.r. There was no loss of stereochemistry at the alkenyl site (i.e., >98:2 *E*:*Z* in all cases).

A notable aspect of the findings in Scheme 2 is that that the sense of enantioselectivty is opposite to that observed when the same set of alkenyl–Al compounds were used in ECA reactions with trisubstituted enones (see Scheme 1a).[7a] As will be described, this trend applies to other additions involving 1,1-disubstituted enone substrates, a mechanistic rationale for which will be provided later in this disclosure.

Next, we probed the addition of a 1,1-disubstituted alkenyl–Al compound, easily prepared by performing the Al–H addition with Ni(dppp)$Cl_2$ (vs. Ni$(PPh_3)_2Cl_2$ for high β selectivity) to enone **5a** (Scheme 3).[8] For this initial transformation **imid-d** proved to be optimal (vs. 85:15 e.r., 76% yield with **imid-a**), affording **8a** in 63% yield and 95:5 enantiomeric ratio (e.r.). However, different sulfonate-containing NHC ligands emerged as the superior choice in subsequent examples.[9] Thus, reactions with more electron-rich or electron-deficient alkenyl–Al compounds proceeded with similar efficiency and enantioselectivity in the presence of **imid-b** or **imid-c** (**8b-d**, Scheme 3). This may be due to the earlier transition state generated with electron-deficient Al compounds; interaction between the substrates and catalyst would thus be diminished, and therefore a more sizable *ortho* substituent in the NHC might be needed for high enantioselectivity (54% yield, 75:25 e.r. and 57% yield, 84:16 e.r. for **8c** and **8d** with **imid-a**). In the case of an electron-donating alkenyl–Al compound, on the other hand, tighter catalyst- substrate association might engender increased steric repulsion when a more conformationally constrained complex is involved (**imid-d**), leading to diminished efficiency (e.g., **8b** was obtained in 34% yield, 91:9 e.r. with **imid-d**). 1,3-Diene **8e**, derived from a process that involved an enyne substrate, and alkenyl silane **8f**, generated from silyl-substituted alkyne, were isolated in 50% and 74% yield and 90.5:9.5 and 99:1 e.r., respectively; the higher stereochemical control with the more sterically hindered alkenyl–Al compound is mechanistically significant. The exceptionally high enantioselectivity (>99:1 e.r.) as well as the possibility of accessing thioester **8i** are noteworthy. The product is sufficiently activated for conversion to various desirable derivatives, such as carboxylic ester,[10] which cannot be directly accessed by an ECA reaction (<5% conv.).

Regarding the need for different NHC ligands to obtain maximum efficiency and/or enantioselectivity, it is important to note that a key attribute of any class of catalysts is whether it is readily modifiable and if different derivatives can be tested for a particular application. While it is possible to use a single complex for every transformation, and this would be the case if the NHC ligand were too cumbersome to modify and include in screening studies, the corresponding results would be inferior.[11]

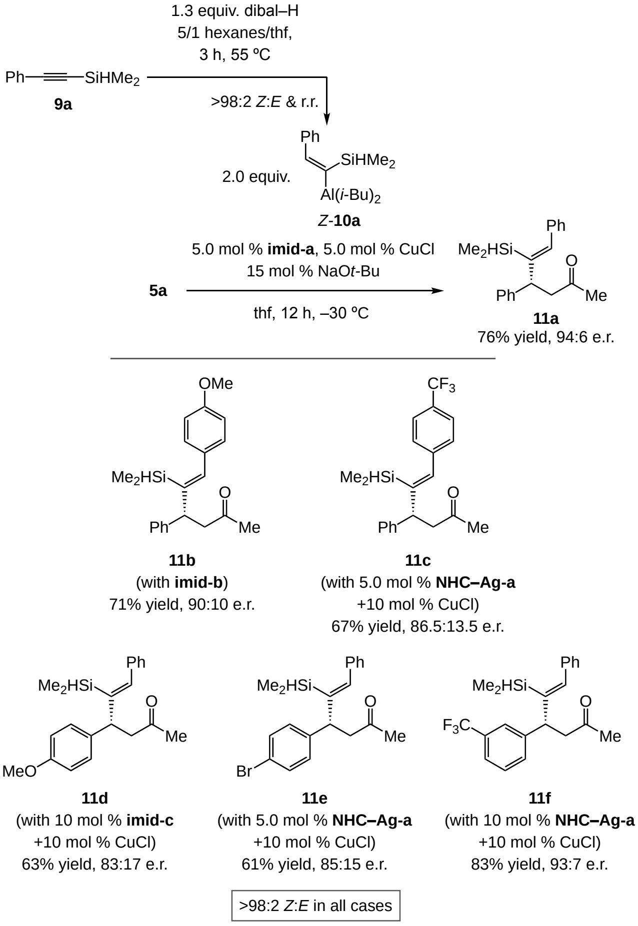


**Scheme 3.** Catalytic ECA with 1,1-disubstituted alkenyl–Al compounds. Reactions were carried out under $N_2$, and yields correspond to isolated and purified products (±5%). Enantiomeric ratios were determined by HPLC analysis (±1%). See the Supporting Information for details.

We then turned our attention to examining catalytic ECA reactions with silyl-substituted alkenyl–Al compounds. We considered this an important aspect of these studies for several reasons. 1) Previous investigations had shown that the presence of a sizeable substituent at the same carbon as the Al can lead to significantly higher enantioselectivity.[7b] 2) Subsequent modification of the alkenyl silane, such as C–Si to C–H conversion to afford *E*- or *Z*-disubstituted alkenyl units[12] or Hiyama-type cross-coupling[13] to give *E*- or *Z*-

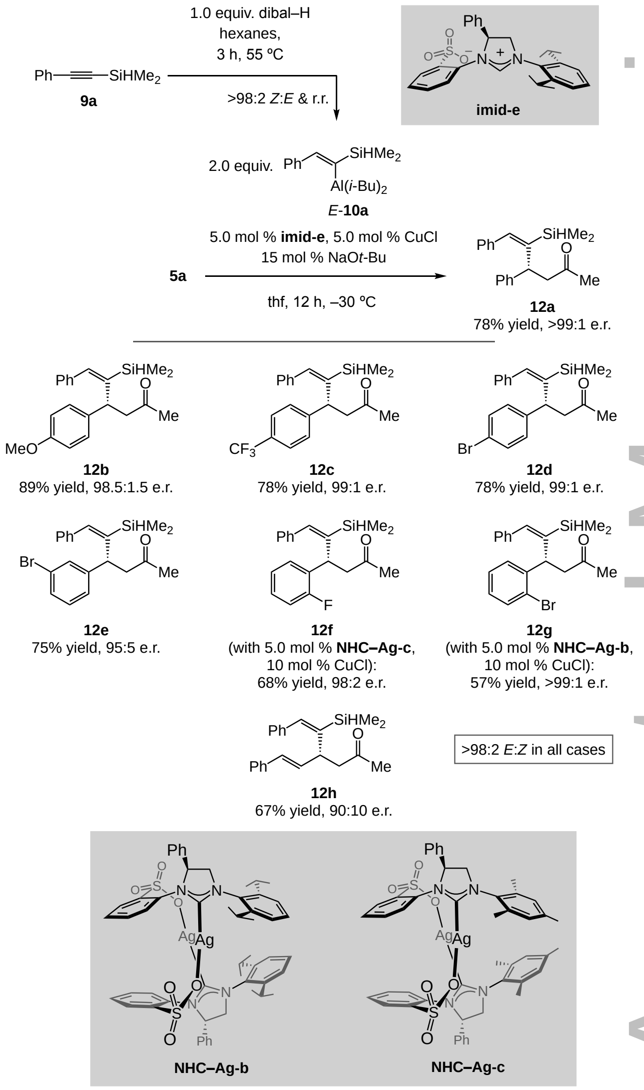
trisubstituted olefinic products would become feasible.

In the event, subjection of silyl-substituted alkyne **9a** to dibal–H (5/1 hexanes/thf, 3 h, 55 °C) led to formation of *Z*-**10a** (Scheme 4),[14] which was used directly for ECA with enone **5a**. Screening studies showed that, in this particular instance, the NHC–Cu complex derived from **imid-a** is optimal, allowing us to isolate **11a** in 76% yield and 94:6 e.r. (>98:2 *Z*:*E*). Additional examples provided in Scheme 4 (**11b-f**), indicate that e.r. values, while at useful levels (83:17–93:7), are generally lower than what we observed for **11a**. Generation of the trimethylsilyl derivatives of the alkenyl–Al compounds is similarly facile but the corresponding ECA reactions afford the expected products in lower yields (competitive *i*-Bu addition; see the Supporting Information for further analysis).



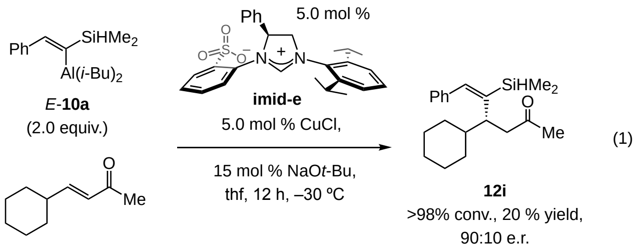
**Scheme 4.** Catalytic ECA with *Z*-trisubstituted alkenyl–Al compounds. Reactions were carried out under $N_2$, and yields correspond to isolated and purified products (±5%). *Z*:*E* ratios were determined by analysis of $^1H$ NMR spectra of unpurified product mixtures (±2%). Enantiomeric ratios were determined by HPLC analysis (±1%). See the Supporting Information for details.

By carrying out the Al–H addition in pure hexanes (vs. 5/1 hexanes/thf), silyl-substituted alkyne **9a** was converted to *E*-**10a** (Scheme 5);[14d] the corresponding ECA with **5a** in the presence of 5.0 mol % of the NHC–Cu complex derived from **imid-e** afforded **12a** in 78% yield and >99:1 e.r. As the additional examples indicate, a variety of different aryl-substituted enones, including those that contain an electron-rich or electron-deficient moiety readily react to afford **12b-g** in 57–89% yield and 90:10 to >99:1 e.r. (Scheme 5). A notable case is the reaction with an α,β,γ,δ-unsaturated ketone that generates 1,4-diene **12h** in 67% yield and 90:10 e.r. As was noted, while **imid-e** is typically optimal, with the more sterically hindered enones (i.e., those that contain an *o*-substituted aryl unit), higher yields were obtained when **NHC–Ag–b-c** were used as catalyst precursors; the reason for this trend is not clear at the present time.



**Scheme 5.** Catalytic ECA with *E*-trisubstituted alkenyl–Al compounds. Reactions were carried out under $N_2$, and yields correspond to isolated and purified products (±5%). *Z*:*E* ratios were determined by analysis of $^1H$ NMR spectra of unpurified product mixtures (±2%). Enantiomeric ratios were determined by HPLC analysis (±1%). See the Supporting Information for details.

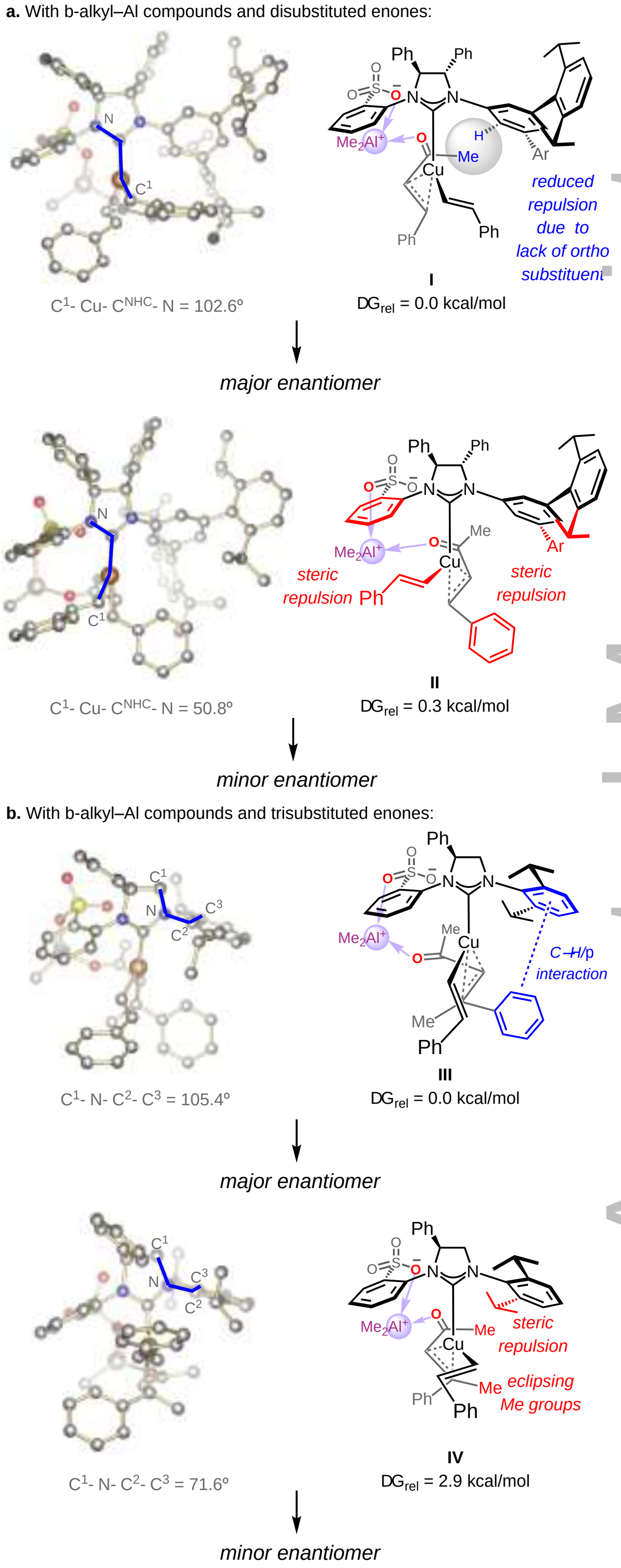
A drawback of the present approach is that ECA with alkyl-substituted enones are inefficient; the example provided in Eq. (1) is representative. The low yield of the desired product might arise from diminished electrophilicity of the enone substrates, rendering alternative reaction pathways too competitive. Development of catalyst and strategies that address this issue thus remains an unresolved issue. However, the present set of transformation are scalable and do not require rigorous exclusion of air and moisture (i.e., a glovebox) to be carried, albeit with some loss in enantioselectivity. For example, 1.0 mmol of **5a** was transformed to **6a** in 65% yield and 90:10 er.



To gain insight regarding the basis for the change in the identity of the major product enantiomer for reactions between β-alkenyl–Al compounds di- (this work) and tri-substituted enones (reported formerly; Scheme 1a),[7a] we performed DFT calculations at the M06–L/def2-TZVPP//M06–L/ def2-SVP level of theory (Scheme 6).[15] As suggested previously for other transformations facilitated by this class of NHC–Cu complexes, a mode of reaction involving a salt bridge between the sulfonate and the enone carbonyl group may be proposed.[16] In the major pathway (**I**) for formation of product **5a** (see Scheme 2) there is minimal repulsion between the methyl ketone unit and the ligands NAr moiety (lack of an *ortho* substituent; Scheme 6a). Moreover, the enone's Ph group is able to avoid generating steric pressure by interaction with the 3,5-(2,6-diisopropylphenyl)phenyl substituent, an unfavorable association that is present in the transition state leading to the minor enantiomer (**II**).[16a]

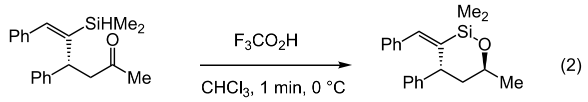
The latter steric pressure forces the NHC ligand to rotate around the Cu–$C^{NHC}$ bond, engendering repulsion between the alkenyl and the aryl sulfonate ligands, as indicated by the contracted $C^1$–Cu–$C^{NHC}$–N dihedral angle (50.8º in **II** vs. 102.6º in **I**). While the free energy for transition state **II** is only marginally larger than that of **I** (0.3 kcal/mol), the aforementioned consideration are expected to be more dominant in the preceding alkene π-complex (contracted $C^1$–Cu–$C^{NHC}$ angle of 106.0º vs. 120.4º in **II**), suggesting that, in the pathway leading to the minor enantiomer, it is olefin coordination that is turnover-limiting.

In the case of additions to trisubstituted enones[7a] it is the opposite substrate rotamer which likely reacts preferentially (**III**, Scheme 6b vs. **I**, Scheme 6a). We expect the mode of addition **III** to be favored because of C–H/π interaction between the substrate Ph ring and the NAr moiety, and also due to the fact that an eclipsing interaction between the substrate's Me groups (see **IV**) can be avoided. Additionally, the methyl ketone moiety in **IV** is oriented to the right, as shown, leading to steric repulsion with the NHC's *o*-*i*-Pr group, and hence the contracted $C^1$–N–$C^2$–$C^3$ dihedral angle (71.6º).



**Scheme 6.** Rationale for reversal of facial selectivity for ECA to di- (this work) and trisubstituted enones (see ref. 7a). Calculations were performed at the M06–L/def2-TZVPP//M06–L/def2-SVP level in dichloromethane as solvent with the use of the SMD solvation model.

In conclusion, we have developed a catalytic method for ECA of a variety of readily accessible alkyl–Al compounds to acyclic β-aryl-substituted, α,β-unsaturated methyl ketones. Most products contain stereochemically defined disubstituted as well as *E*-, or *Z*- trisubstituted alkenyl moieties that may be functionalized in a number of ways. The latter attributes are perhaps best highlighted by the representative diastereoselective reduction/siloxane formation, shown in Eq. (2).[17]



**12a**
78% yield, >99:1 e.r.

**13**
73% yield, >95:5 d.r.

## Experimental Section

*Procedure for NHC–Cu-catalyzed conjugate addition with an alkenyl–Al compound*: A flame-dried 1-dram vial containing a magnetic stir bar was charged with **imid-e** (2.7 mg, 0.005 mmol), NaO*t*-Bu (1.4 mg, 0.0150 mmol), and CuCl (0.5 mg, 0.005 mmol) under $N_2$ atm in a glovebox. The vessel was sealed (septum), removed from the glovebox, after which thf (0.5 mL) was added and the solution was allowed to stir for 15 min. A 1 M solution of *E*-**10a** in hexanes (200 μL, 0.200 mmol) was then added and the mixture was allowed to cool to −78 °C. A solution of 4-phenyl-3-buten-2-one **5a** (17.6 mg, 0.100 mmol) in thf (0.5 mL) was added by syringe. The mixture was allowed to stir at −30 °C for 12 h and then warm to 22 °C. At this point, the reaction was then quenched by the addition of a saturated aqueous solution of sodium-potassium tartrate (3 mL) and the mixture was washed with $Et_2O$ (3 × 1 mL). The combined organic layers were filtered through a short plug of silica gel ($Et_2O$), the volatiles were removed in vacuo and the dark oil residue was purified by silica gel chromatography (hexanes to 20:1 hexanes:$Et_2O$) to afford **12a** (24.1 mg, 0.078 mmol, 78% yield, >98:2 *E*:*Z*, >99:1 e.r.).

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## COMMUNICATION

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