

Enantioselective Catalysis

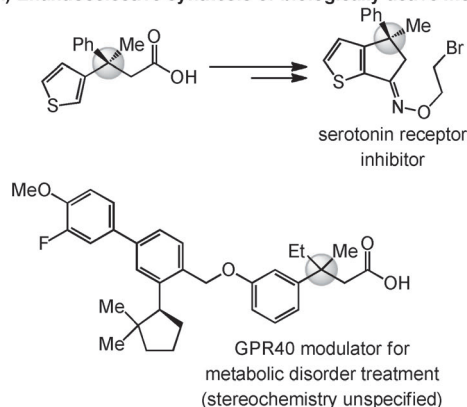
# Enantioselective Synthesis of Quaternary Carbon Stereogenic Centers through Copper-Catalyzed Conjugate Additions of Aryl- and Alkylaluminum Reagents to Acyclic Trisubstituted Enones\*\*

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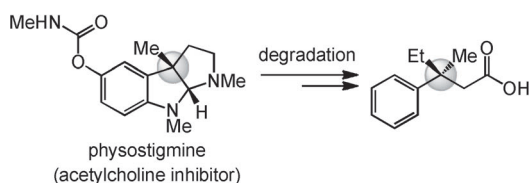
Development of methods for efficient catalytic enantioselective conjugate addition (ECA) of readily accessible carbon-based nucleophiles to  $\alpha,\beta$ -unsaturated carbonyls is a major objective of research in chemical synthesis.<sup>[1]</sup> Progress has been made in designing effective chiral complexes that promote a variety of catalytic ECA reactions. One especially challenging area corresponds to transformations that furnish all-carbon quaternary stereogenic centers;<sup>[2]</sup> recent years have witnessed a number of important advances in this regard,<sup>[3–6]</sup> including applications to synthesis of complex natural products.<sup>[7]</sup> Nonetheless, several important limitations remain. One shortcoming is that the majority of processes relate to reactions with cyclic systems.<sup>[4–7]</sup> The paucity of ECA processes that involve acyclic trisubstituted substrates might be because their transformations, unlike those of cyclic enones, are not facilitated by ring strain; catalysts shown to be effective in differentiating the enantiotopic faces of a *Z* cyclic olefin might not provide optimal enantioselectivity with commonly used linear *E* alkenes. The limited number of cases involving acyclic substrates<sup>[3]</sup> correspond to incorporation of alkyl groups or highly activated Meldrum acid derivatives.<sup>[3b–d]</sup> There is one report of enantioselective Rh-catalyzed ECA of acyclic enoates with sodium tetraarylborates (one aryl unit transferred);<sup>[8]</sup> in a recent disclosure, three related examples of Pd-catalyzed ECA with  $\text{PhB}(\text{OH})_2$  are shown to proceed in up to 80:20 enantiomeric ratio (e.r.).<sup>[6c]</sup> Another study relates to Cu-catalyzed ECA of methyl units to acyclic  $\alpha,\beta$ -unsaturated aryl- or heteroaryl-substituted ketones; in all but one case (with  $\text{Et}_3\text{Al}$ ),  $\text{Me}_3\text{Al}$  was used.<sup>[9]</sup>

The value of catalytic ECA processes that allow for incorporation of aryl and different alkyl groups is demonstrated in Scheme 1. A carbonyl group with a  $\beta$ -stereogenic center substituted with a phenyl and a thienyl group has been utilized in enantioselective preparation of a serotonin receptor inhibitor;<sup>[10]</sup> another example is the agent against metabolic disorder.<sup>[11]</sup> Access to a related enantiomerically enriched carboxylic acid, but one that carries two alkyl and an aryl unit at its quaternary carbon stereogenic site, was

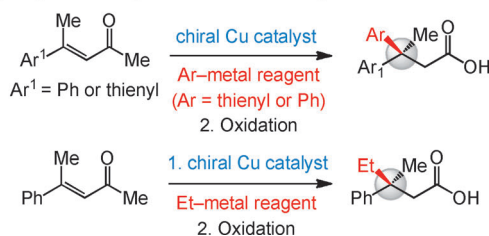
## A) Enantioselective synthesis of biologically active molecules



## B) Determination of absolute stereochemistry of biologically active molecules



## C) Required catalytic enantioselective processes:



**Scheme 1.** Catalytic ECA of acyclic enones to afford all-carbon quaternary stereogenic centers can be applied to the total synthesis of biologically active molecule and/or facilitate the elucidation of their absolute stereochemical identity.

required to ascertain the absolute stereochemistry of acetylcholine esterase inhibitor physostigmine.<sup>[12]</sup>

Herein, we report the first Cu-catalyzed method for efficient ECA of aryl and commonly occurring alkyl groups to a range of trisubstituted acyclic enones. Arylaluminum reagents are easily prepared in situ from aryllithium species and commercially available dialkylaluminum halides; trialkylaluminum reagents are inexpensive. A robust chiral bidentate N-heterocyclic carbene (NHC) of silver and commercially available  $\text{Cu}(\text{OTf})_2$  are combined to form the chiral catalyst (0.5–3.0 mol %; 0.5–24 h); products are formed in 33–95 % yield and 90:10 to >99:1 e.r. It should be noted

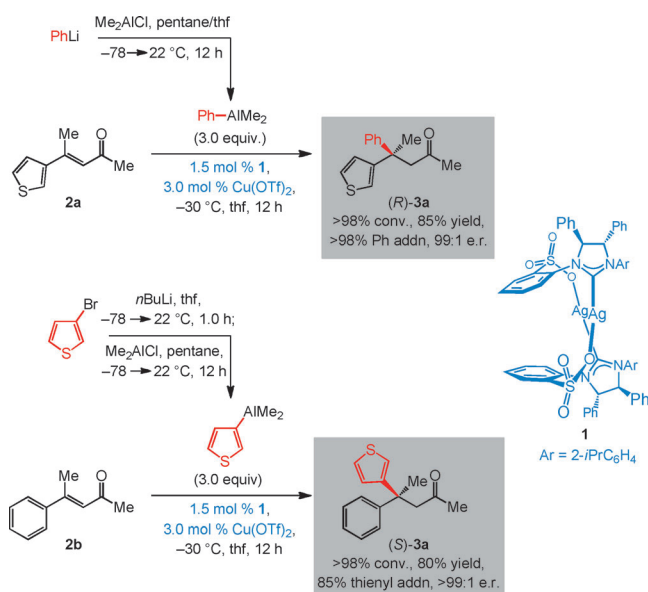
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that, although efficient catalytic enantioselective allylic substitutions (EAS) with the same types of organoaluminum reagents have been reported,<sup>[13]</sup> ECA processes present a distinct challenge for several reasons. In both cases, nucleophilic addition of an organocopper intermediate is likely followed by reductive elimination; the first key step, however, is reversible only in ECA, requiring C–C bond formation to be sufficiently rapid. Moreover, the relative position of the alkene and the phosphate or carbonyl unit in EAS and ECA processes, respectively, are different; such factors are significant in reactions that likely involve association of the Lewis basic groups with the catalytic complex.<sup>[14]</sup>

We began by exploring the possibility of accessing the thienyl-containing ketone, used in the synthesis of a serotonin receptor inhibitor (Scheme 1), by an efficient enantioselective ECA. We thus established that treatment of enone **2a** with three equivalents of Ph(Me)<sub>2</sub>Al, generated in situ from reaction of PhLi and Me<sub>2</sub>AlCl, and 3.0 mol % of an



**Scheme 2.** Preparation of aryl(dimethyl)aluminum reagents and their in situ use in NHC–Cu-catalyzed ECA reactions with trisubstituted enones to generate all-carbon quaternary stereogenic centers.

NHC–Cu catalyst derived from Ag complex **1** and Cu(OTf)<sub>2</sub><sup>[15]</sup> leads to the formation of (R)-**3a** in 85% yield and 99:1 e.r. (Scheme 2). Reaction is complete in 12 h at –30 °C without generating any detectable amount of byproducts derived from Me transfer.<sup>[13]</sup> As further depicted in Scheme 2, we evaluated the possibility of performing an enantioselective ECA with the corresponding thienyl-aluminum reagent and phenyl-substituted  $\alpha,\beta$ -unsaturated ketone **2b**. Under the latter conditions, the transformation proceeds to complete conversion in 12 h, affording (S)-**3a** in 80% yield and >99:1 e.r.; however, there is 15% of the achiral product derived from Me transfer.<sup>[16]</sup> The NHC–Cu complex derived from **1**,

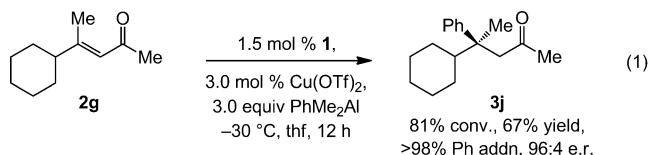
**Table 1:** NHC–Cu-catalyzed ECA with various aryl(dimethyl)aluminum reagents.<sup>[a]</sup>

$\text{Ar}^1-\text{C}(\text{Me})=\text{C}(\text{Me})-\text{C}(=\text{O})\text{Me} \xrightarrow[\text{3.0 mol \% Cu(OTf)}_2, \text{3.0 equiv ArMe}_2\text{Al}]{\text{1.5 mol \% 1, } -30^\circ\text{C, thf, 12 h}} \text{Ar}^1-\text{C}(\text{Me})_2-\text{C}(=\text{O})\text{Me}$						
Entry	Ar <sup>1</sup>	Ar	Product	Conv. [%] <sup>[b]</sup> Yield [%] <sup>[c]</sup>	Ar vs. Me addn <sup>[b]</sup>	e.r. <sup>[d]</sup>
1	2-thienyl; <b>2c</b>	Ph	<b>3b</b>	73; 57	>98:2	92:8
2	<i>o</i> -FC <sub>6</sub> H <sub>4</sub> ; <b>2d</b>	Ph	<b>3c</b>	88; 33	55:45	>99:1
3	<i>p</i> -F <sub>3</sub> CC <sub>6</sub> H <sub>4</sub> ; <b>2e</b>	Ph	<b>3d</b>	89; 76	92:8	94:6
4	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ; <b>2f</b>	Ph	<b>3e</b>	>98; 82	>98:2	98:2
5	Ph; <b>2b</b>	<i>p</i> F <sub>3</sub> CC <sub>6</sub> H <sub>4</sub>	<b>3f</b>	>98; 82	92:8	98:2
6	Ph; <b>2b</b>	<i>p</i> MeOC <sub>6</sub> H <sub>4</sub>	<b>3g</b>	>98; 77	>98:2	>99:1
7	3-thienyl; <b>2a</b>	<i>p</i> F <sub>3</sub> CC <sub>6</sub> H <sub>4</sub>	<b>3h</b>	>98; 83	>98:2	96:4
8	3-thienyl; <b>2a</b>	<i>p</i> MeOC <sub>6</sub> H <sub>4</sub>	<b>3i</b>	>98; 89	>98:2	>99:1

[a] Reactions were performed under N<sub>2</sub> atmosphere. [b] Determined through analysis of 400 MHz <sup>1</sup>H NMR spectra of unpurified mixtures. [c] Yield of isolated and purified products. [d] Determined by HPLC analysis ( $\pm$  2%); see the Supporting Information for details.

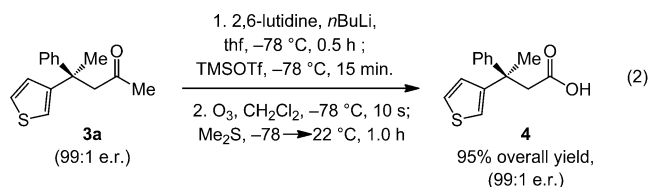
which emerged as the superior choice, has not been previously employed.<sup>[13]</sup>

A range of trisubstituted enones and in situ generated aryl(dialkyl)aluminum reagents can be used (Table 1). Reaction involving 2-thienyl-substituted **2c** (vs. 3-substituted **2a**, Scheme 2) with Ph(Me)<sub>2</sub>Al leads to 73% conversion in 12 h (entry 1), and **3b** is isolated in 57% yield with complete transfer of the phenyl unit in 92:8 e.r. Formation of the sterically demanding stereogenic center that contains two aryl groups is relatively sluggish when one bears an *ortho* unit; the example in entry 2 is illustrative (17% conv. with the derived *ortho* chloroaryl substrate). Synthesis of *ortho*-fluoroaryl **3c** thus proceeds in 33% yield and is accompanied by the product derived from Me transfer (Ph:Me 55:45); however, the ECA remains exceptionally enantioselective (>99:1 e.r.). Cu-catalyzed ECA with enones that contain electron-deficient or electron-rich aryl units proceed efficiently and with high enantioselectivity: **3d** and **3e** are obtained in 76% and 82% yield, with 92% and >98% group selectivity and in 94:6 and 98:2 e.r., respectively (entries 3 and 4). Similarly high efficiency and enantioselectivity is observed with aryl-(dimethyl)aluminum reagents that carry electron-withdrawing or -donating groups (entries 5–8). The example in Equation (1), regarding formation of **3j** in 67% yield, >98% transfer of Ph group and 96:4 e.r., demonstrates that catalytic ECA can be performed with high selectivity with enones that contain only alkyl substituents.



Access to the corresponding enantiomerically enriched carboxylic acid derivatives increases the value of the protocol (cf. Scheme 1); nonetheless, our attempts to identify conditions for efficient ECA with related derivatives (e.g., Weinreb

amides, *N*-acyloxazolidinones, carboxylic esters, thioesters) proved unsuccessful (< 10% conv.). To address the above problem, we identified a two-step procedure that can be completed in less than 2 h, without the need for purification of the silyl enol ether intermediate, to obtain the derived carboxylic acid; the example leading to **4** in 95% yield is representative [Eq. (2)].



We subsequently turned our attention to catalytic ECA with  $\text{Et}_3\text{Al}$  (Table 2), of which a single example exists involving the transformation of a phenyl ketone.<sup>[9]</sup> We therefore established that aryl- and heteroaryl-substituted enones of different steric and electronic attributes can be used

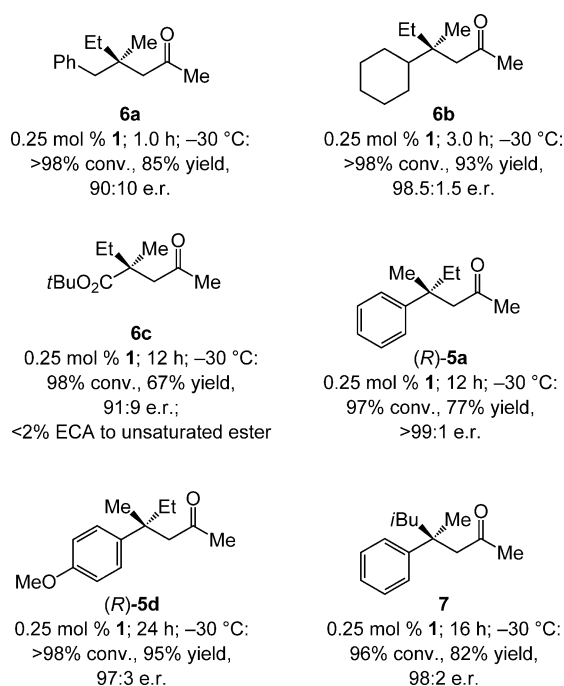
**Table 2:** NHC-Cu-catalyzed ECA of aryl-substituted enones with  $\text{Et}_3\text{Al}$ .<sup>[a]</sup>

Entry	Ar; Substrate	Product	<i>t</i> [h]	Conv. [%] <sup>[b]</sup> ; Yield [%] <sup>[c]</sup>	e.r. <sup>[d]</sup>
1	Ph; <b>2b</b>	<b>5a</b>	0.5	> 98; 93	98:2
2	2-thienyl; <b>2c</b>	<b>5b</b>	1.0	> 98; 86	98.5:1.5
3	<i>p</i> -F <sub>3</sub> CC <sub>6</sub> H <sub>4</sub> ; <b>2e</b>	<b>5c</b>	1.0	> 98; 89	99:1
4	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ; <b>2f</b>	<b>5d</b>	1.0	> 98; 92	99:1
5	2-naphthyl; <b>2h</b>	<b>5e</b>	2.5	97; 94	97.5:2.5
6	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub> ; <b>2i</b>	<b>5f</b>	12	98; 87	> 99:1
7	<i>m</i> -FC <sub>6</sub> H <sub>4</sub> ; <b>2j</b>	<b>5g</b>	3.0	> 98; 90	96.5:3.5

[a] Reactions were performed under N<sub>2</sub> atmosphere. [b] Determined through analysis of 400 MHz <sup>1</sup>H NMR spectra of unpurified mixtures. [c] Yield of isolated and purified products. [d] Determined by GC analysis (entries 1 and 2) or HPLC analysis (± 2%); see the Supporting Information for details.

in transformations that require 0.5 mol% of the NHC-Cu complex to proceed to ≥ 97% conversion, affording the desired products in 96.5:3.5 to > 99:1 e.r. It is noteworthy that, in contrast to ECA with the sterically more demanding aryl(dimethyl)aluminum reagents, additions to substrates that possess relatively large substituents, such as a 2-naphthyl or an *ortho*-bromo unit (entries 5 and 6 of Table 2), proceed to ≥ 97% conversion with equally high enantioselectivities as the less hindered acyclic enones.

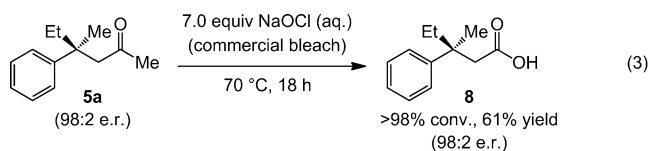
The products shown in Scheme 3 underscore several vital characteristics of the approach. Processes involving  $\text{Et}_3\text{Al}$  that lead to the formation of **6a** and **6b** demonstrate that dialkyl-substituted enones can be used; the lower e.r. in the case of **6a** (90:10 vs. 98.5:1.5 for **6b**) is likely due to a diminished degree of differentiation between a Me and a benzyl group (vs. a cyclohexyl). Enantioselective synthesis of **6c**, a product that contains two functionalizable and



**Scheme 3.** Representative cases of efficient and enantioselective NHC-Cu-catalyzed ECA reactions with  $\text{Et}_3\text{Al}$  and non-aryl-substituted enones as well as with  $\text{Me}_3\text{Al}$  and  $(i\text{Bu})_3\text{Al}$  reagents.

differentiable carbonyl groups, illustrates that addition to the site β to the ketone unit, versus to the carboxylic ester, is exclusive in spite of formation of a more hindered quaternary carbon stereogenic center. Representative reactions with  $\text{Me}_3\text{Al}$  are shown in Scheme 3 as well; *(R)*-**5a** and *(R)*-**5d** are obtained in 77% and 95% yield and > 99:1 and 97:3 e.r., respectively. Enantioselective synthesis of isobutyl-substituted ketone **7**, generated in 82% yield and 98:2 e.r., shows that the NHC-Cu-catalyzed protocol can be extended to ECA with  $(i\text{Bu})_3\text{Al}$ , another commercially available organoaluminum species the ECA of which has not been reported with trisubstituted acyclic enones.

In addition to the efficient two-step protocol depicted in Equation (2), ECA products without a relatively sensitive heterocyclic substituent prone to adventitious oxidation (such as **3a**)<sup>[17]</sup> can be converted directly to the desired carboxylic acids in a single step with commercial bleach.<sup>[18]</sup> The transformation in Equation (3), resulting in the formation of enantiomerically enriched **8** in 61% yield (98:2 e.r.) is illustrative (cf. Scheme 1).



Development of additional catalytic ECA protocols and applications to complex molecule synthesis are in progress.

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