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N-Heterocyclic Carbene–Cu-Catalyzed Enantioselective Conjugate Additions with Alkenylboronic Esters as Nucleophiles

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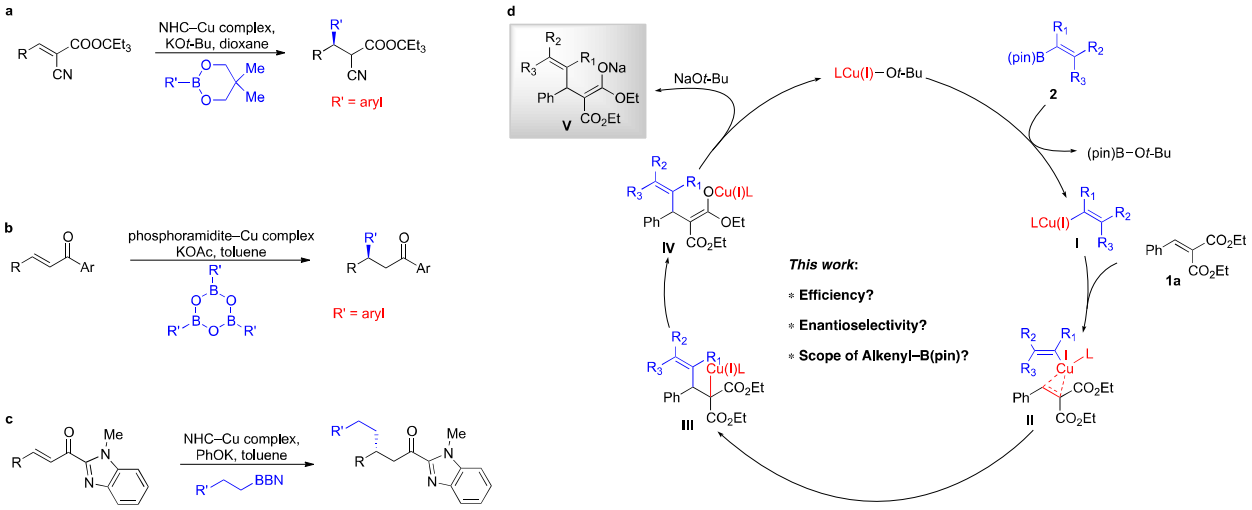
ABSTRACT: Catalytic enantioselective conjugate additions with easily accessible alkenylboronic acid pinacol esters as nucleophiles promoted by chiral copper complexes of N-heterocyclic carbenes are presented. These processes constitute an unprecedented instance of conjugate additions of a variety of functionalized alkenyl groups and afford desired products that are otherwise difficult-to-access in up to 98% yield and 99.5:0.5 enantiomeric ratio. The origins of ligand-controlled enantioselectivity are elucidated with density functional theory (DFT) calculations.

KEYWORDS: Conjugate addition, copper catalysis, alkenylboron, enantioselective catalysis, N-heterocyclic carbene

Introduction

Copper-catalyzed enantioselective conjugate additions of organometallic reagents to α,β-unsaturated compounds stand for a powerful method for efficient and selective construction of C–C bonds.[1] Reactions with highly reactive organometallic reagents such as Grignard reagents,[1c-f, 1l, 2] organozinc reagents[1b, 1g, 1h, 3] and organoaluminum,[1c-i, 4] organozirconium reagents[1k, 5] have been well established. In contrast, the utility of more robust nucleophiles has been much less studied. Organoboronic acids and their derivatives are attractive due to their high functional group tolerance and diversity, low toxicity and ease of access and handling. There are only two reports regarding Cu-catalyzed enantioselective 1,4-conjugate additions with arylboronic acid derivatives by Hayashi (Scheme 1a)[6] and Zhou (Scheme 1b)[7]. In addition, Sawamura disclosed the use of organoboranes as nucleophiles in Cu-catalyzed enantioselective conjugate additions (Scheme 1c).[8]



Scheme 1. Cu-Catalyzed Enantioselective Conjugate Additions with Organoboron Nucleophiles.

Introduction of an alkenyl group into α,β-unsaturated compounds is desirable in organic synthesis. Although Rh-catalyzed enantioselective conjugate additions with organoboron compounds have been well studied,[1j-k] alkenylboron compounds still stands for a class of challenging nucleophiles. To the best of our knowledge, there is no protocol for highly efficient and enantioselective conjugate additions of alkenylboron nucleophiles promoted by Cu-based catalysts.[9] Herein, we describe the first catalytic enantioselective 1,4-additions of alkenylboronic acid pinacol esters to enoates promoted by N-heterocyclic carbene (NHC)–Cu complexes.

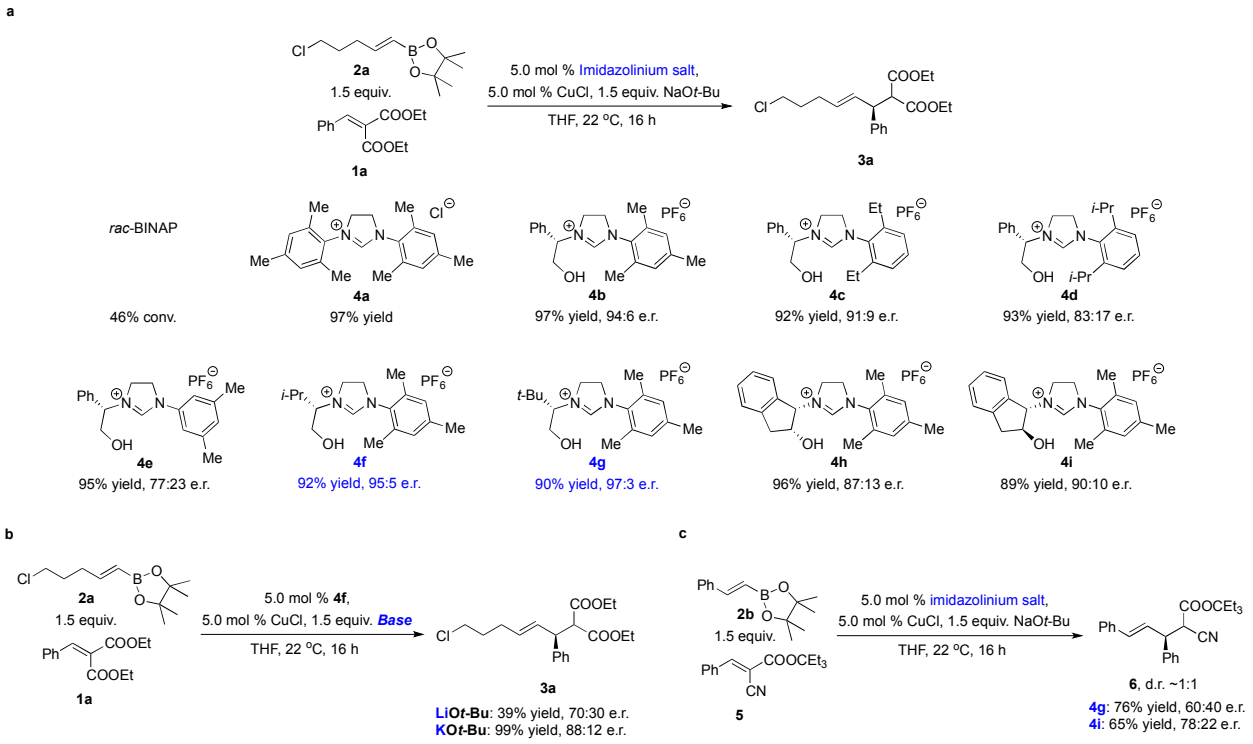
We envision that a suitable Cu(I) complex could promote transmetallation with alkenyl–B(pin) to generate alkenyl–Cu complex **I**, which could coordinate with diethyl benzylidenemalonate **1a** to form a π-complex **II**. Transfer of alkenyl group to the π-bond would deliver the Cu(I) complex **III**, which rapidly collapsed to Cu enolate **IV**. Exchange of **IV** with NaO*t*-Bu released addition product **V** and regenerated the catalyst. (Scheme 1d)

The challenge for reactions with alkenylboron nucleophiles is their lower reactivity. In addition, the metal salts that are present in the reactions with more reactive Grignard reagents, organozinc reagents and organoaluminum reagents might work as Lewis acids to activate α,β-unsaturated compounds and lead to more organized transition states, resulting in higher reactivity and better control of enantioselectivity.[4g, 10] Such activation is significantly diminished in the case of alkenylboronic esters as nucleophiles due to their weaker Lewis acidity. Therefore, ligands that are strong σ-donor might be necessary to enhance the nucleophilicity of alkenylcopper intermediate.[11]

Results and discussion

In our initial investigation, reactions of commercially available alkenyl–B(pin) (pin = pinacolato) **2a** with ethyl cinnamate in the presence of NHC–Cu or bisphosphine–Cu complexes resulted in <2% conversion of starting materials. More electronically deficient ethyl benzylidenemalonate **1a** was tested. Transformation of **1a** with alkenyl–B(pin) **2a** catalyzed by *rac*-BINAP–Cu complex led to 46% conversion of **1a**, indicating σ-donation of the bisphosphine ligand is not strong enough to promote the alkenyl addition (Scheme 2a). Follow-up studies revealed that **1a** did undergo efficient conjugate addition with **2a** in the presence of NHC–Cu complex derived from imidazolinium salt **4a**, affording desired product **3a** in 97% yield.

Having established the viability of Cu-catalyzed conjugate addition of alkenyl–B(pin) to alkylidene malonates, we turned our attention to the development of an enantioselective variant (Scheme 2a).

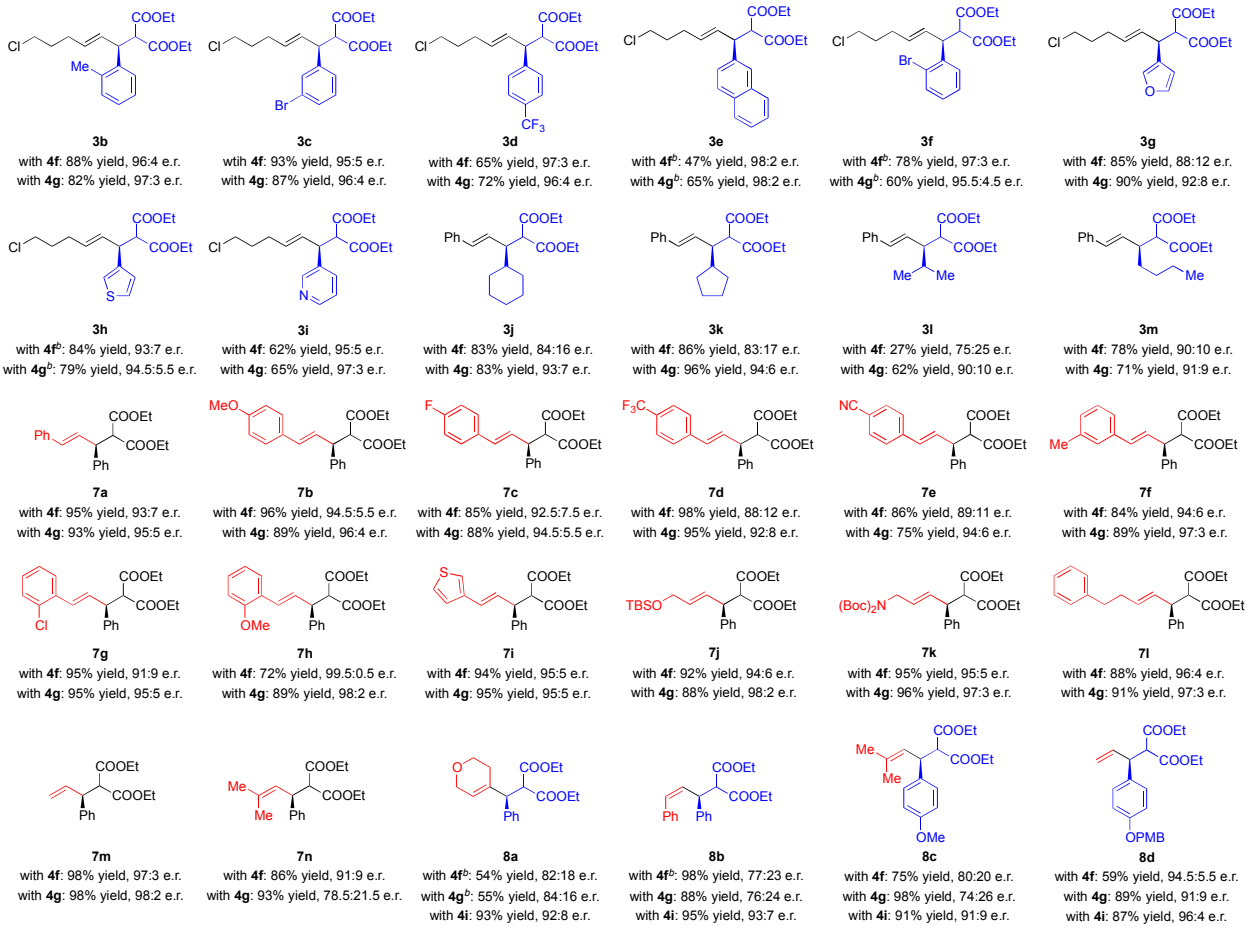


Scheme 2. Optimization of Reaction Conditions[a]

[a]Reactions were performed under N_2 atmosphere; enantiomeric ratios (e.r.) were determined by HPLC analysis, see Supporting Information for details.

Reaction of enoate **1a** with alkenyl–B(pin) **2a** was carried out in the presence of NHC–Cu complex in situ generated from imidazolinium salt **4b**. Under these conditions, desired product **3a** was delivered in 97% yield and 94:6 e.r.. Modification of the N–aryl moiety by increasing the size of the 2,6-substituents resulted in diminished enantioselectivity (cf. **4c**-**d**). Reaction catalyzed by Cu complex derived from imidazolinium salt **4e** bearing 3,5-substituents provided **3a** in 95% yield and 77:23 e.r.. Follow-up studies revealed that changing the amino-alcohol moiety of the ligand from phenylglycinol to valinol and *tert*-leucinol led to improvement of enantioselectivity (cf. **4f**-**g**). Cu complexes derived from imidazolinium salts **4h** and **4i** containing two stereogenic centers promoted the reaction to deliver **3a** in 87:13 and 90:10 e.r. respectively. In addition, Na^+ is important for high enantioselectivity. Reactions of enoate **1a** and alkenyl–B(pin) **2a** in the presence of LiO*t*-Bu and KO*t*-Bu led to erosion of enantioselectity (Scheme 2b). Further investigation indicates that reaction of cyanoester **5** that provides high enantioselectivity in Hayashi's work in the presence of NHC–Cu complexes derived from imidazolinium salts **4g** and **4i** resulted in significantly lower enantioselectivity (Scheme 2c). One prominent aspect of this protocol is that the imidazolinium salts **4f**-**g** are air-stable solids, and can be readily prepared in multi-gram quantities from inexpensive materials and without costly silica gel column chromatography purifications.[12] Moreover, the reactions with alkenyl–B(pin) proceed in high efficiency and enantioselectivity at ambient temperature. Costly and inconvenient cryogenic conditions are avoided.

With the optimal conditions in hand, we first investigated the scope of enoates (Scheme 3). Reactions in the presence of imidazolinium salt **4f** or **4g** were carried out, providing conjugate addition products in similar enantioselectivity. Transformations of enoates bearing sterically hindered aryl groups afforded desired products in high yield and selectivity (cf. **3b** and **3f**),



Scheme 3. Substrate Scope[a]

[a] Same conditions as shown in Scheme 2. [b] 10 mol % Imidazolinium salts and CuCl were used.

although 10 mol % catalyst loading is necessary in the case of formation of **3f**. Aryl-substituted enoates containing electron-withdrawing groups can be converted into products in 60–93% yield and 95:5–97:3 e.r. (cf. **3c-d**, **3f**). Halogen substituents are well tolerated in the reaction

conditions (cf. **3c** and **3f**). Reactions with both electron-rich and electron-deficient hetero-aryl substituents generated products in 62–90% yield and 88:12–97:3 e.r. (cf. **3g-i**). In these cases, Cu complex derived from **4g** gives slightly higher enantioselectivity. Enoates that contain primary and secondary alkyl substitutent are also suitable substrates, delivering products without significant erosion of enantioselectivity (cf. **3j**-**m**).

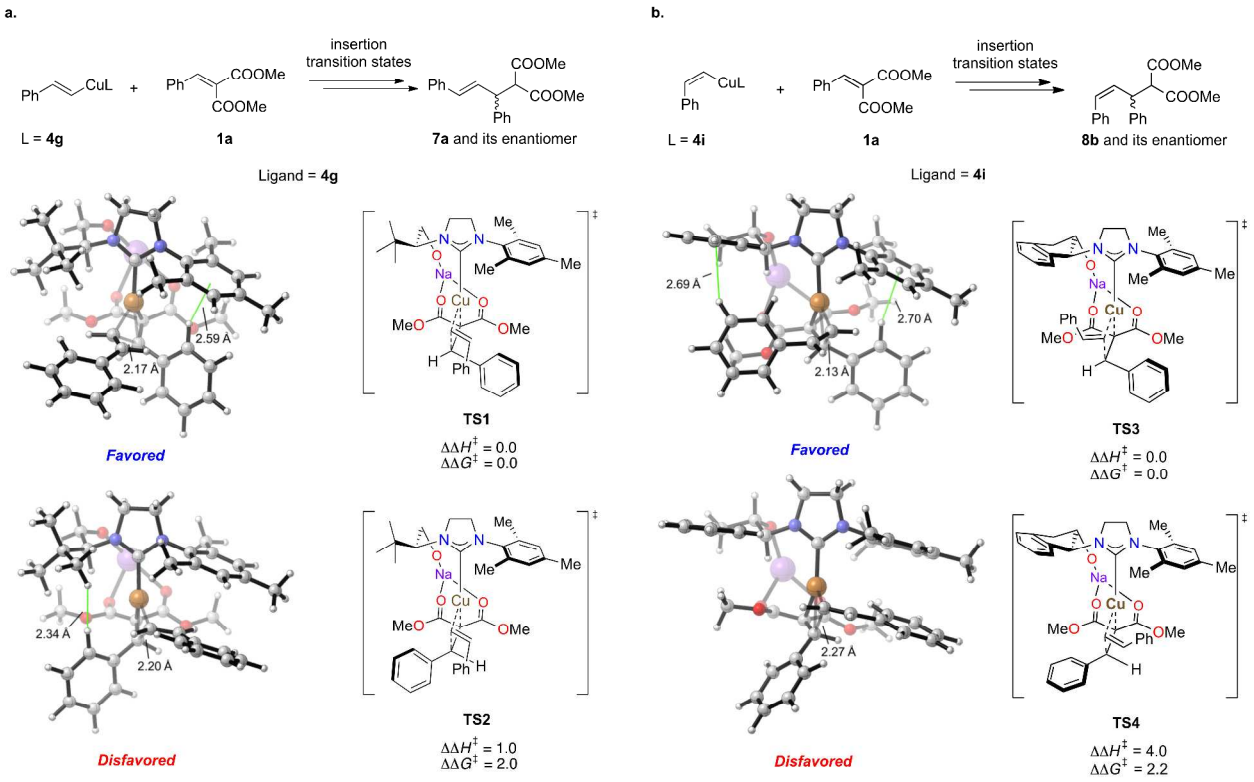
Next, the scope of alkenyl–B(pin) was studied (Scheme 3). Reactions with alkenylboron compounds bearing *E*-1,2-disubstituted alkene moieties afforded addition products in 75–98% yield and 88:12–99.5:0.5 e.r. (cf. **7a-n**). In most cases, Cu complex derived from imidazolinium salt **4g** induces similar enantioselectivity with that formed from **4f**. Transformations of alkenyl–B(pin) that contain electron-donating (**7b-c**, **7f**, **7h**) and electron-withdrawing (**7d-e**, **7g**) aryl groups provided products in high yield and enantioselectivity. Heteroaryl-substituted alkenyl–B(pin) are good substrates (**7i**). Alkyl-substituted alkenyl–B(pin) were converted into products in up to 96% yield and 98:2 e.r. (cf. **7j-l**). Protected amine and alcohol are well tolerated. We also investigated simple vinyl–B(pin) as nucleophile; product **7m** was generated in 98% yield and 97:3 e.r. and 98:2 e.r. in the presence of **4f** and **4g** respectively. Reactions with commercially available 1,2,2-trisubstituted alkenyl–B(pin) afforded addition product **7n** in high efficiency, whereas in this case Cu complex formed from imidazolinium salt **4f** induced much higher enantioselectivity.

Other substitution patterns of alkenyl–B(pin) nucleophiles were investigated. However, ligands optimized for *E*-1,2-disubstituted alkenyl–B(pin) proved to be not selective. In addition, reactions with enoates bearing electron-donating groups resulted in lower enantioselectivity under previous conditions. Therefore, further ligand optimization is necessary for development of highly enantioselective conjugate additions.

Reinvestigation of Cu complexes derived from imidazolinium salts shown in Scheme 2a revealed that NHC–Cu complex in situ generated from imidazolinium salt **4i** promoted the reactions with higher enantioselectivity. As shown in Scheme 3, transformations of 1,1,2-trisubstituted and *Z*-1,2-disubstituted alkenyl–B(pin) afforded **8a** and **8b** in much higher enantioselectivity (92:8 and 93:7 e.r.) in the presence of NHC–Cu complex prepared from imidazolinium salt **4i**. Furthermore, enoates bearing electron-donating aryl groups can be converted into products in higher selectivity (cf. **8c**-**d**). It is worth mentioning that such alkenyl groups are otherwise difficult to introduce through reactions with Grignard reagents, organozinc reagents or organoaluminum reagents. These results indicated that the enantioselectivity of NHC–Cu-catalyzed enantioselective conjugate additions with alkenyl–B(pin) is highly sensitive to the substitution patterns of the alkenyl groups. Ligand optimization is necessary according to different substrate combinations.

To understand the origins of ligand-controlled enantioselectivity, we studied the determining olefin insertion transition states with DFT calculations at the ωB97X-D/6-311+G(d,p)-SMD(THF)//ωB97X-D/6-31G(d) level.[13] The optimized structures and relative enthalpies and free energies of transition states for the insertion with *E*-vinyl copper species and ethyl benzylidenemalonate **1a**, **TS1** and **TS2**, are summarized in Scheme 4a.[14] The sodium bridge model is adapted from previous computational studies.[9] This is also supported by the results that reactions in the presence of LiO*t*-Bu and KO*t*-Bu provide lower enantioselectivity (Scheme 2b). In addition, the diethyl ester moiety is important for formation of the sodium bridge. This explains why reaction of cyanoester **5** led to low enantioselectivity (Scheme 2c). For ligand **4g, TS1**, which leads to the major enantiomer product **7a**, is 2.0 kcal/mol more favorable than **TS2**

in terms of free energy. This is consistent with the experimental enantioselectivity (95:5, Scheme 3). The favored transition state **TS1** has a CH-π interaction[15] between the malonate phenyl C-H



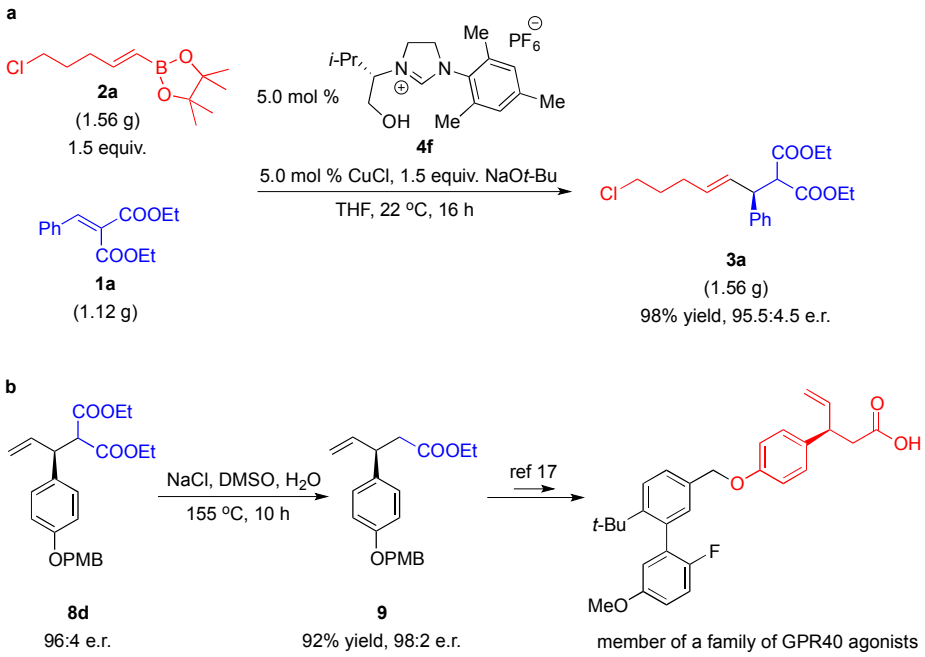
Scheme 4. Mechanistic Studies

and the mesityl group of ligand **4g** (highlighted with green line in **TS1**). This CH-π interaction does not exist in the competing **TS2**, and **TS2** has steric repulsions between the malonate phenyl group and the bulky *t*Bu group of the ligand. Thus, ligand **4g** prefers to have the malonate phenyl group proximal to the mesityl group of the ligand, making **TS1** the favorable transition state and eventually generating enantiomer **7a**.

The ligand **4i** provided the highest enantioselectivity for reactions with *Z*-1,2-disubstituted alkenyl–B(pin) (cf. **8b**, Scheme 3). The computed energy differences of the competing transition states with *Z*-vinyl copper species and ethyl benzylidenemalonate **1a** reproduced the trends in

experiments (Scheme 4b). **TS3** has unique dual CH-π interactions. Both phenyl groups of the substrates have the appropriate proximity to achieve the CH-π interaction with the ligand. This significantly stabilizes **TS3**, making ligand **4i** achieve the highest enantioselectivity for *Z*-olefins among the tested ligands.

The reaction can be conducted on multi-gram scale. As shown in Scheme 5a, reaction of ethyl benzylidenemalonate **1a** (1.12 g) with alkenyl–B(pin) **2a** (1.56 g) in the presence of NHC–Cu complex derived from imidazolinium salt **4f** afforded **3a** in 98% yield and 95.5:4.5 e.r.. Decarboxylation of the conjugate addition products was studied. Treatment of **8d** with NaCl in DMSO and H_2O at 155 ^oC generated decarboxylation product **9** in 92% yield, which constitutes products resulted from a formal enantioselective alkenyl conjugate additions to α,β-unsaturated esters that have been unprecedented (Scheme 5b).[16] Ester **10** was transformed into a member of a family of GPR40 agonists was delivered after several functional group manipulations. Previous method for installation of the stereogenic center is resolution of racemic mixture.[17] The advantage of such catalytic enantioselective protocol is that diversified alkenyl groups with various functional groups can be easily introduced, which is of importance in leading compounds discovery for pharmaceutical molecules.



Scheme 5. Gram Scale Reaction and Application

Conclusion

In conclusion, we have disclosed the first NHC–Cu-catalyzed enantioselective conjugate additions of readily available alkenyl–B(pin) to α,β-unsaturated compounds that can be prepared in a single step. The reactions are performed at ambient temperature in the presence of NHC–Cu complexes in situ generated from easily accessible air-stable imidazolinium salts. Alkenyl groups with a variety of substitution patterns and functional groups can be introduced into products in high efficiency and enantioselectivity. The enantiomerically enriched products may serve as precursors to other useful derivatives that would otherwise be difficult to prepare. The models for enantioselective induction were investigated through DFT calculations, illustrating the selectivity with different catalysts and the unique way of stereogenicity induction of the catalysts that distinguishes our catalytic system from the previous.[6, 12] Development of conjugate additions with other organoboron nucleophiles is underway.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications websites.

Experimental procedures, spectroscopic data, and the NMR spectra of all the products (PDF)

Crystallographic data for **7a** (CIF)

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Notes

The authors declare no conflict of interest.

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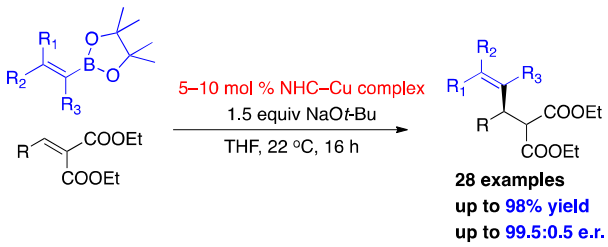
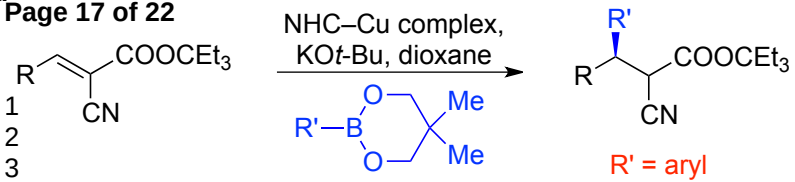
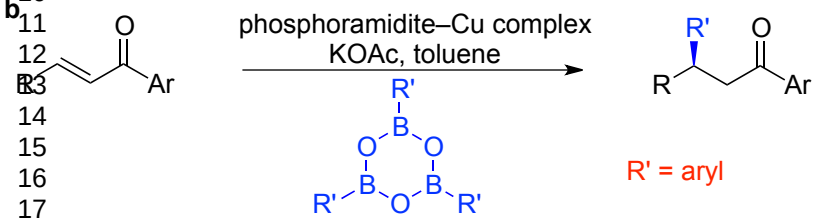
TOC



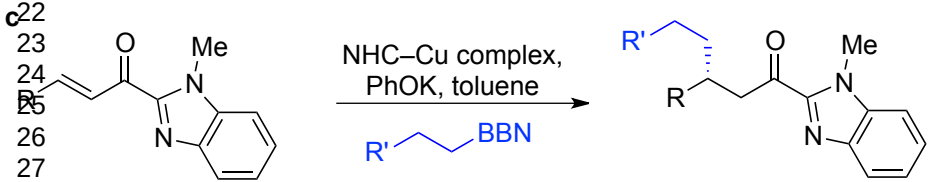
a


NHC–Cu complex,
KO*t*-Bu, dioxane
R' = aryl

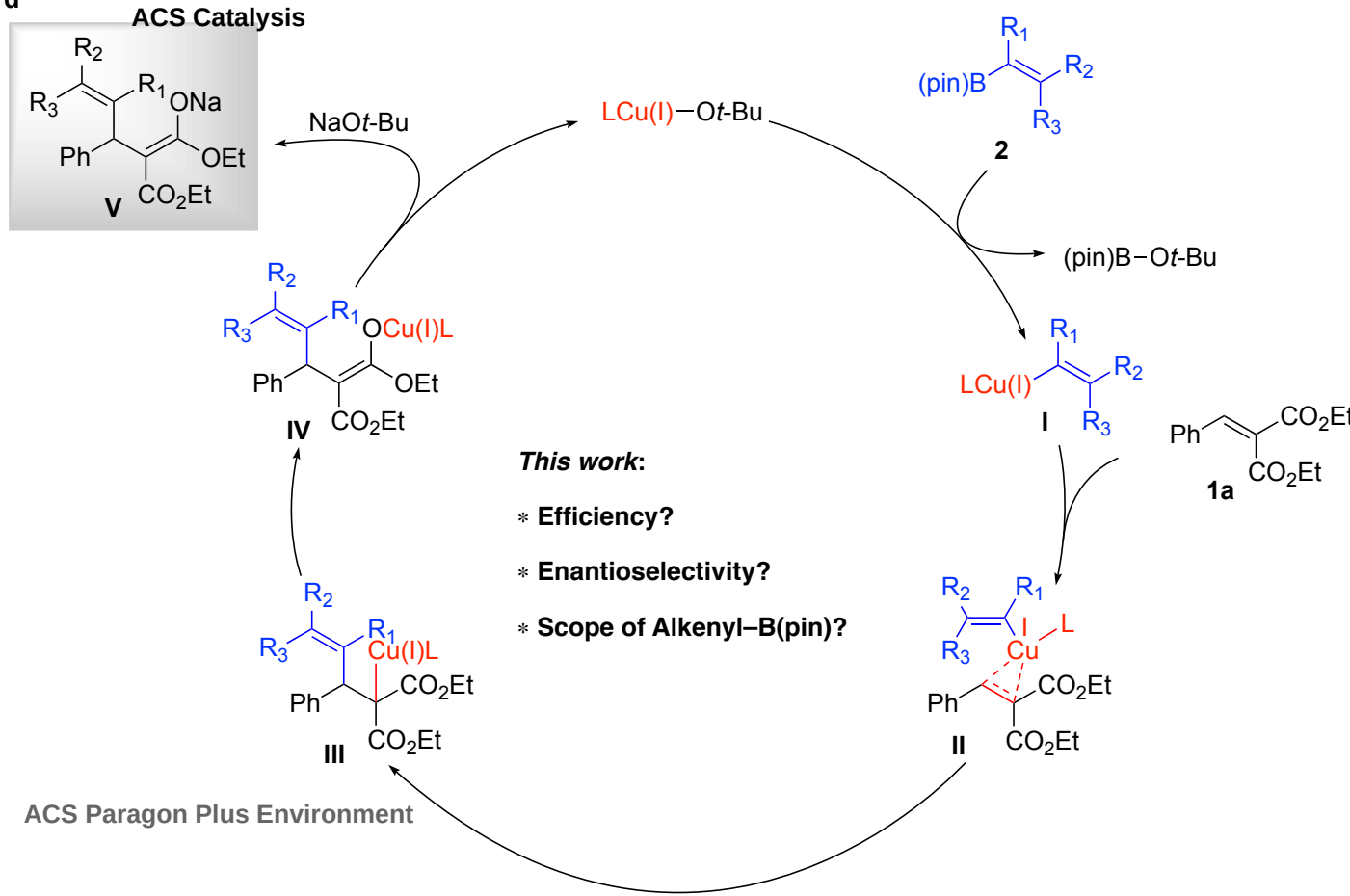
b


phosphoramidite–Cu complex
KOAc, toluene
R' = aryl

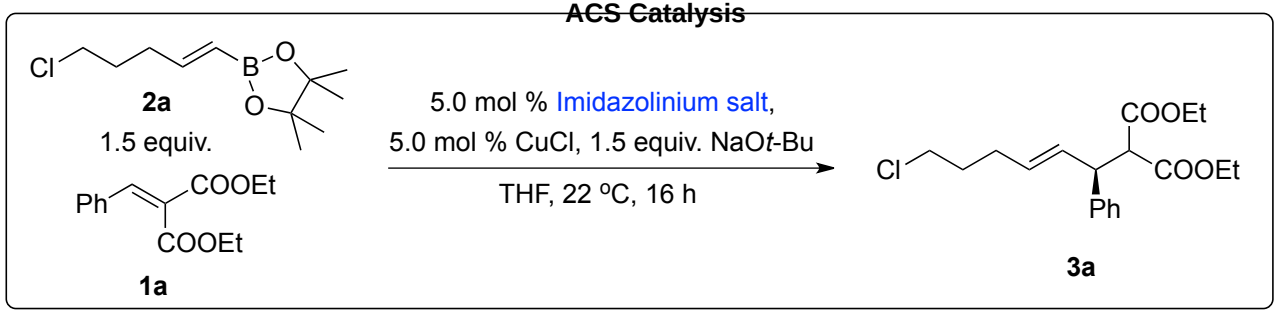
c


NHC–Cu complex,
PhOK, toluene

d

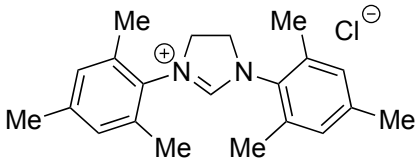

ACS Catalysis
V
NaO*t*-Bu
LCu(I)–O*t*-Bu
2
(pin)B–O*t*-Bu
IV
I
1a
III
II
This work:
∗ Efficiency?
∗ Enantioselectivity?
∗ Scope of Alkenyl–B(pin)?
ACS Paragon Plus Environment

a



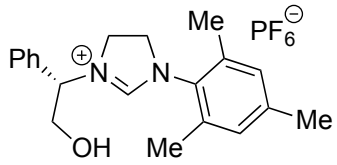
rac-BINAP

46% conv.



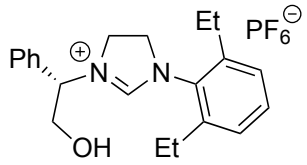
4a

97% yield



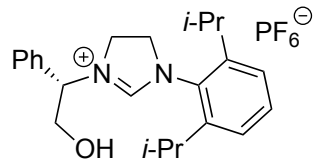
4b

97% yield, 94:6 e.r.



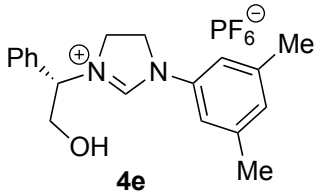
4c

92% yield, 91:9 e.r.



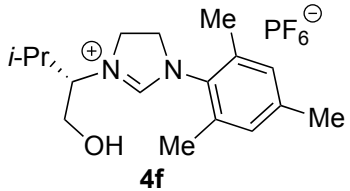
4d

93% yield, 83:17 e.r.



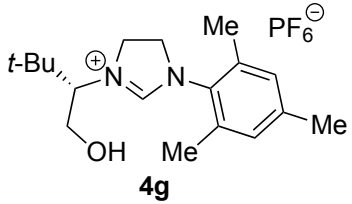
4e

95% yield, 77:23 e.r.



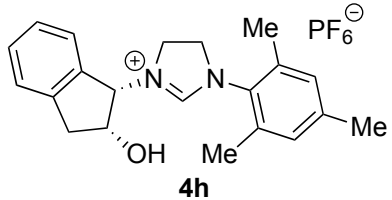
4f

92% yield, 95:5 e.r.



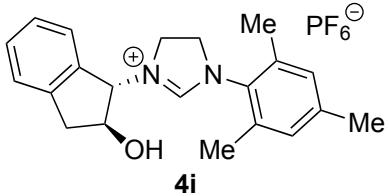
4g

90% yield, 97:3 e.r.



4h

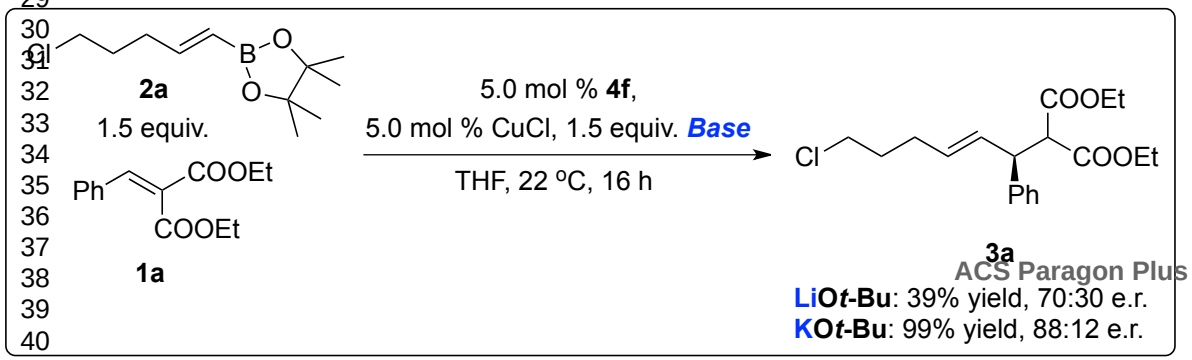
96% yield, 87:13 e.r.



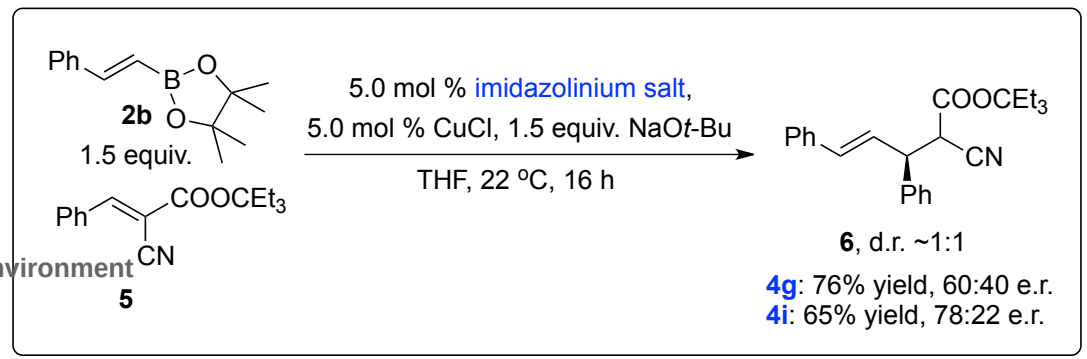
4i

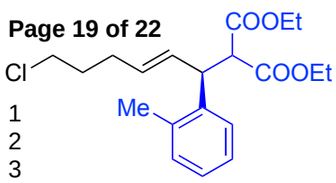
89% yield, 90:10 e.r.

b



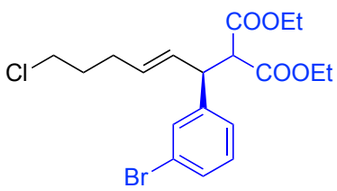
c





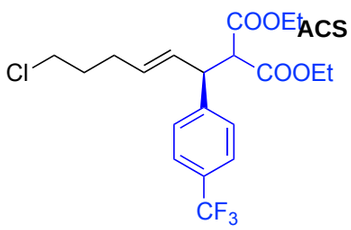
3b

with **4f**: 88% yield, 96:4 e.r.
with **4g**: 82% yield, 97:3 e.r.



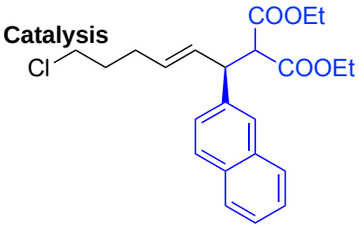
3c

wtih **4f**: 93% yield, 95:5 e.r.
with **4g**: 87% yield, 96:4 e.r.



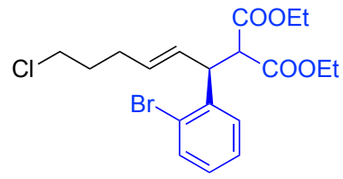
3d

with **4f**: 65% yield, 97:3 e.r.
with **4g**: 72% yield, 96:4 e.r.



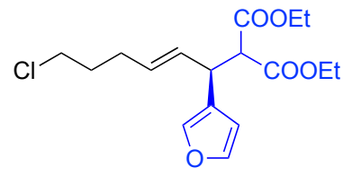
3e

with **4f**^{b}: 47% yield, 98:2 e.r.
with **4g**^{b}: 65% yield, 98:2 e.r.



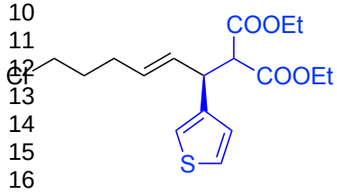
3f

with **4f**^{b}: 78% yield, 97:3 e.r.
with **4g**^{b}: 60% yield, 95.5:4.5 e.r.



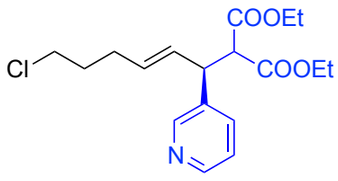
3g

with **4f**: 85% yield, 88:12 e.r.
with **4g**: 90% yield, 92:8 e.r.



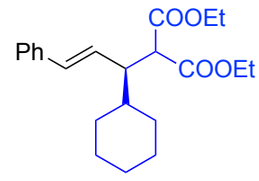
3h

with **4f**^{b}: 84% yield, 93:7 e.r.
with **4g**^{b}: 79% yield, 94.5:5.5 e.r.



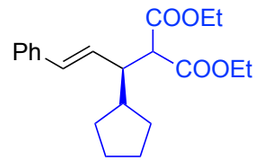
3i

with **4f**: 62% yield, 95:5 e.r.
with **4g**: 65% yield, 97:3 e.r.



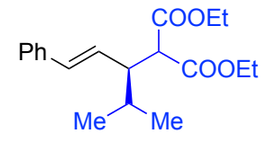
3j

with **4f**: 83% yield, 84:16 e.r.
with **4g**: 83% yield, 93:7 e.r.



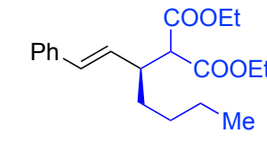
3k

with **4f**: 86% yield, 83:17 e.r.
with **4g**: 96% yield, 94:6 e.r.



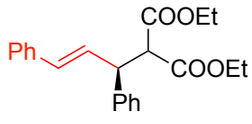
3l

with **4f**: 27% yield, 75:25 e.r.
with **4g**: 62% yield, 90:10 e.r.



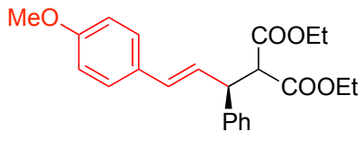
3m

with **4f**: 78% yield, 90:10 e.r.
with **4g**: 71% yield, 91:9 e.r.



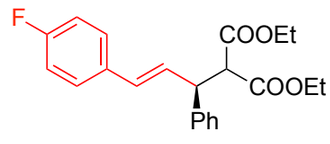
7a

with **4f**: 95% yield, 93:7 e.r.
with **4g**: 93% yield, 95:5 e.r.



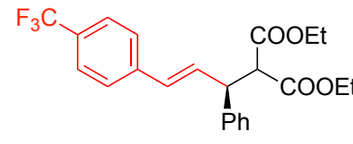
7b

with **4f**: 96% yield, 94.5:4.5 e.r.
with **4g**: 89% yield, 96:4 e.r.



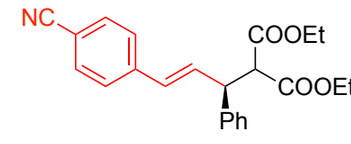
7c

with **4f**: 85% yield, 92.5:7.5 e.r.
with **4g**: 88% yield, 94.5:5.5 e.r.



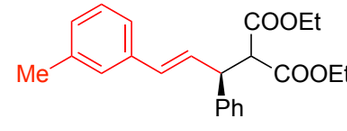
7d

with **4f**: 98% yield, 88:12 e.r.
with **4g**: 95% yield, 92:8 e.r.



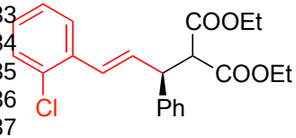
7e

with **4f**: 86% yield, 89:11 e.r.
with **4g**: 75% yield, 94:6 e.r.



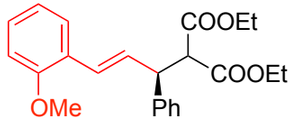
7f

with **4f**: 84% yield, 94:6 e.r.
with **4g**: 89% yield, 97:3 e.r.



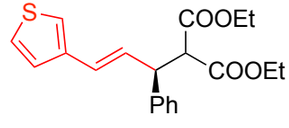
7g

with **4f**: 95% yield, 91:9 e.r.
with **4g**: 95% yield, 95:5 e.r.



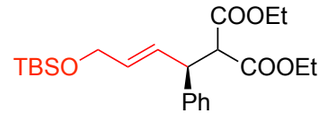
7h

with **4f**: 72% yield, 99.5:0.5 e.r.
with **4g**: 89% yield, 98:2 e.r.



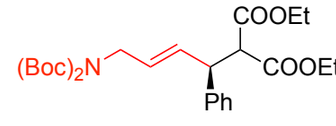
7i

with **4f**: 94% yield, 95:5 e.r.
with **4g**: 95% yield, 95:5 e.r.



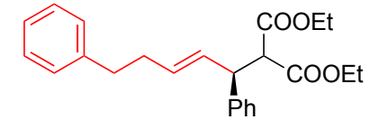
7j

with **4f**: 92% yield, 94:6 e.r.
with **4g**: 88% yield, 98:2 e.r.



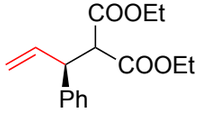
7k

with **4f**: 95% yield, 95:5 e.r.
with **4g**: 96% yield, 97:3 e.r.



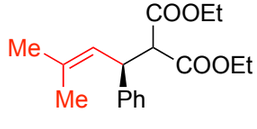
7l

with **4f**: 88% yield, 96:4 e.r.
with **4g**: 91% yield, 97:3 e.r.



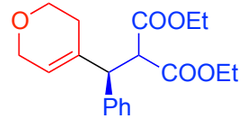
7m

with **4f**: 98% yield, 97:3 e.r.
with **4g**: 98% yield, 98:2 e.r.



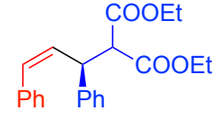
7n

with **4f**: 86% yield, 91:9 e.r.
with **4g**: 93% yield, 78.5:21.5 e.r.



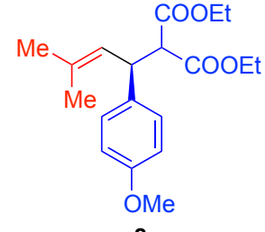
8a

with **4f**^{b}: 54% yield, 82:18 e.r.
with **4g**^{b}: 55% yield, 84:16 e.r.
with **4i**: 93% yield, 92:8 e.r.



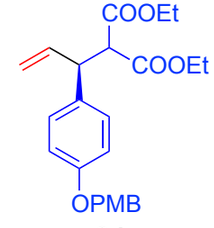
8b

with **4f**^{b}: 98% yield, 77:23 e.r.
with **4g**: 88% yield, 76:24 e.r.
with **4i**: 95% yield, 93:7 e.r.



8c

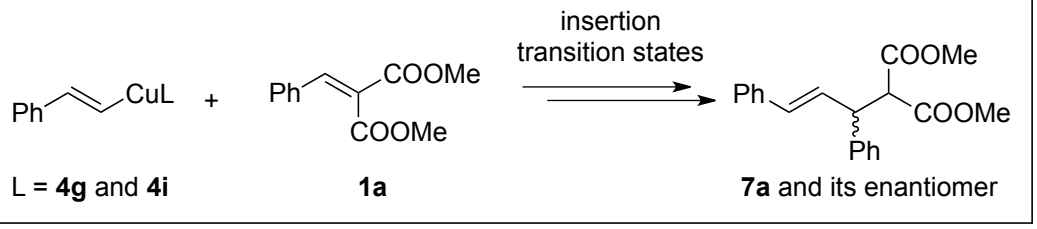
with **4f**: 75% yield, 80:20 e.r.
with **4g**: 98% yield, 74:26 e.r.
with **4i**: 91% yield, 91:9 e.r.



8d

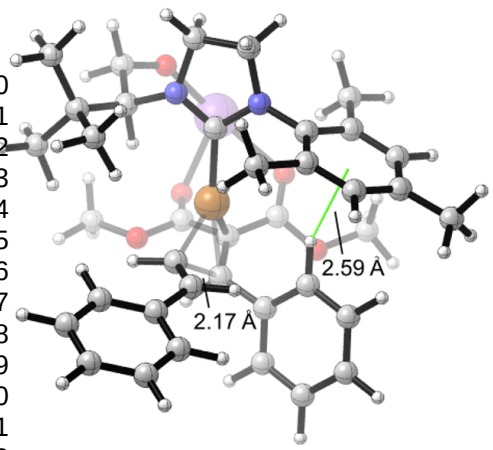
with **4f**: 59% yield, 94.5:5.5 e.r.
with **4g**: 89% yield, 91:9 e.r.
with **4i**: 87% yield, 96:4 e.r.

a.

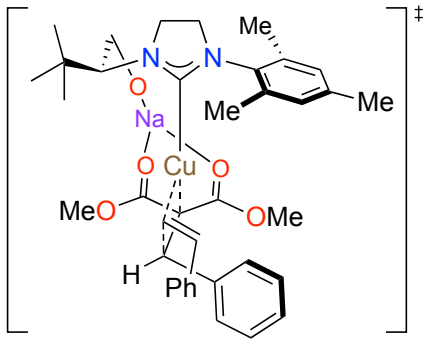


L = **4g** and **4i** **1a** **7a** and its enantiomer

Ligand = **4g**

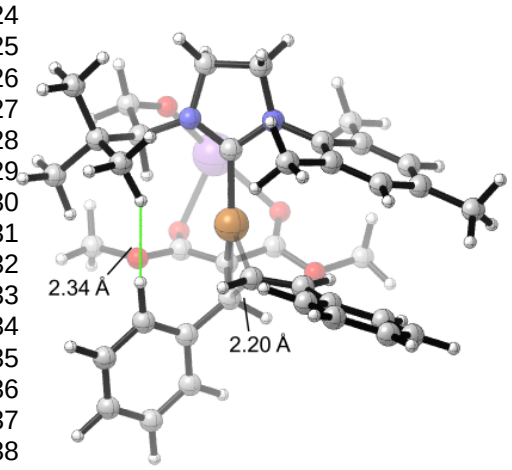


Favored

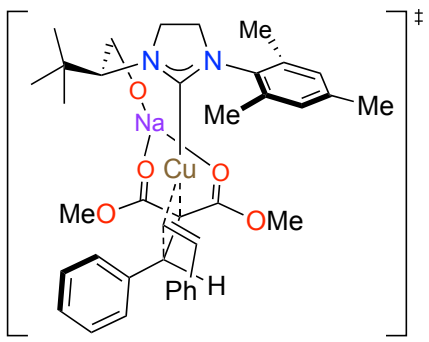


TS1

$\Delta\Delta H^{\ddagger} = 0.0$
$\Delta\Delta G^{\ddagger} = 0.0$



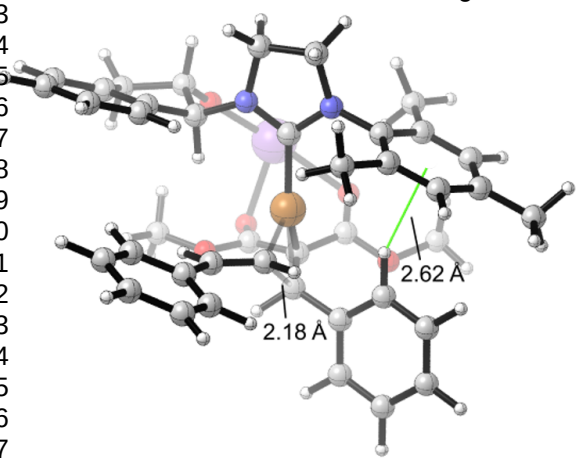
Disfavored



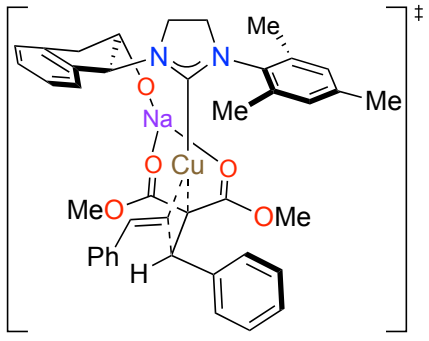
TS2

$\Delta\Delta H^{\ddagger} = 1.0$
$\Delta\Delta G^{\ddagger} = 2.0$

Ligand = **4i**

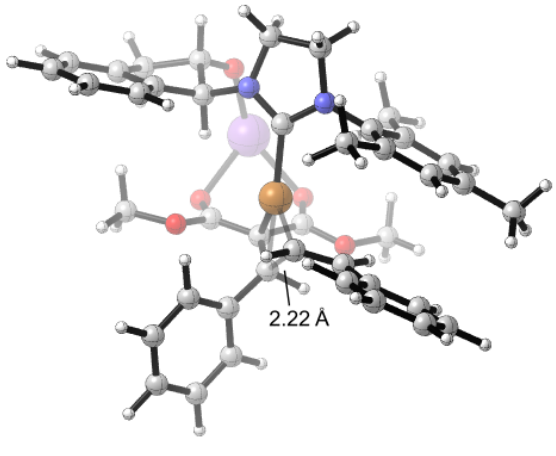


Favored

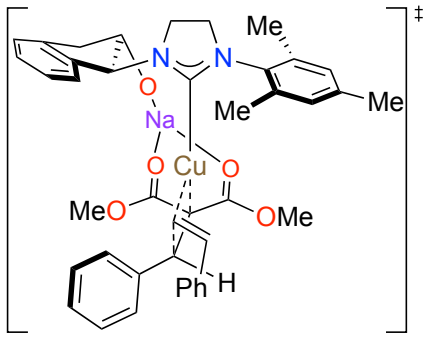


TS3

$\Delta\Delta H^{\ddagger} = 0.0$
$\Delta\Delta G^{\ddagger} = 0.0$



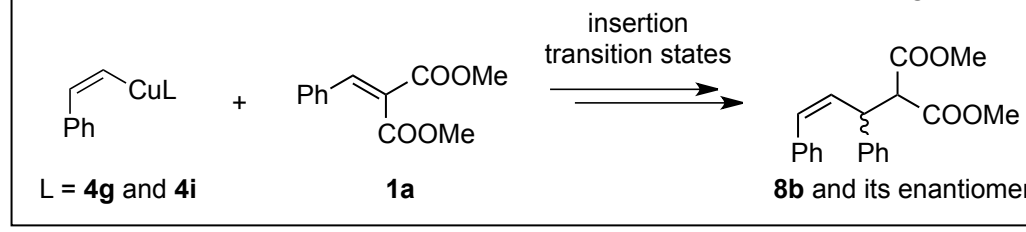
Disfavored



TS4

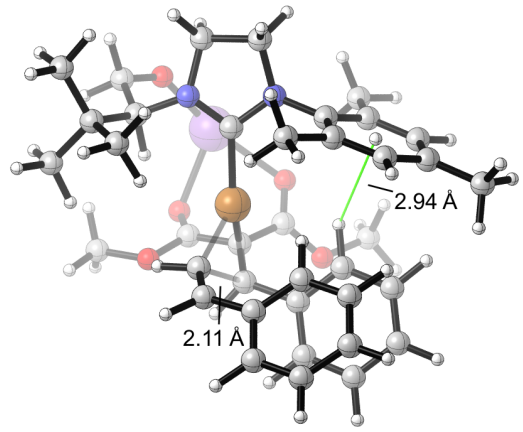
$\Delta\Delta H^{\ddagger} = 0.0$
$\Delta\Delta G^{\ddagger} = 1.0$

b.

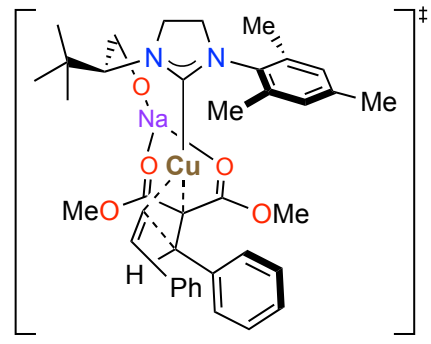


L = **4g** and **4i** **1a** **8b** and its enantiomer

Ligand = **4g**

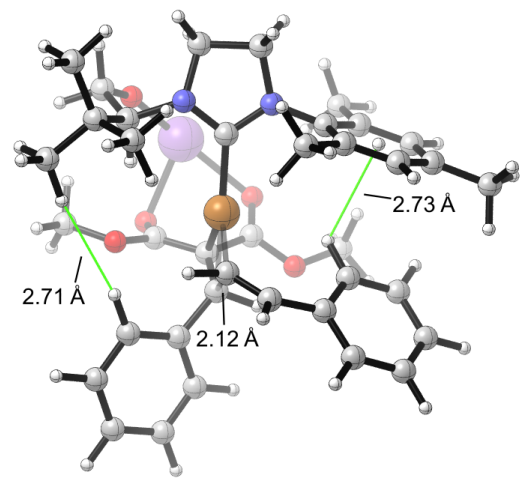


Disfavored

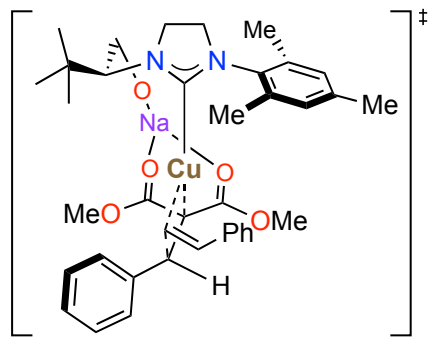


TS5

$\Delta\Delta H^{\ddagger} = 0.0$
$\Delta\Delta G^{\ddagger} = 0.0$



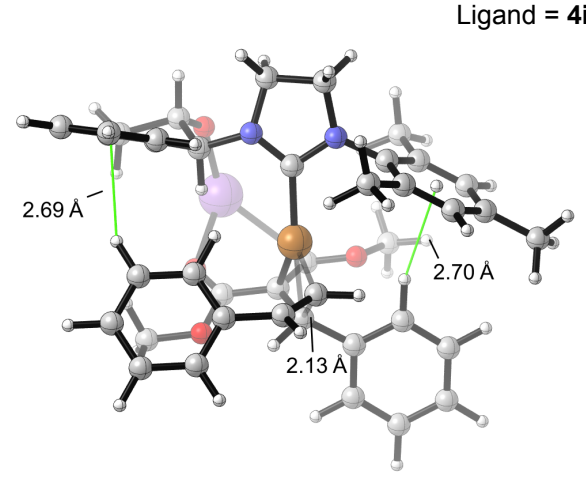
Favored



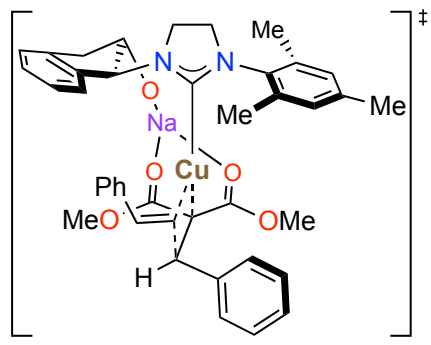
TS6

$\Delta\Delta H^{\ddagger} = -2.3$
$\Delta\Delta G^{\ddagger} = -2.2$

Ligand = **4i**

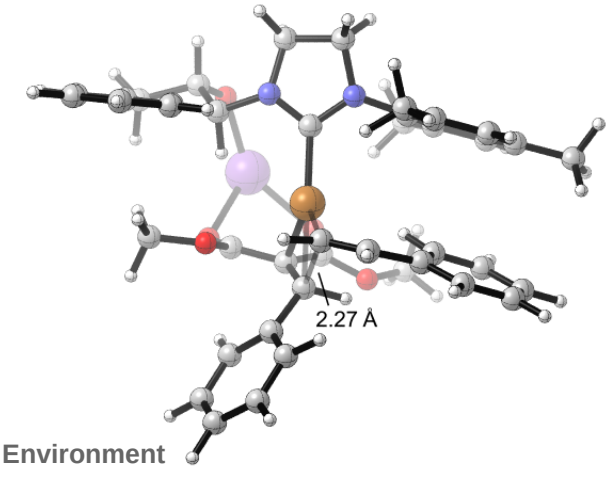


Favored

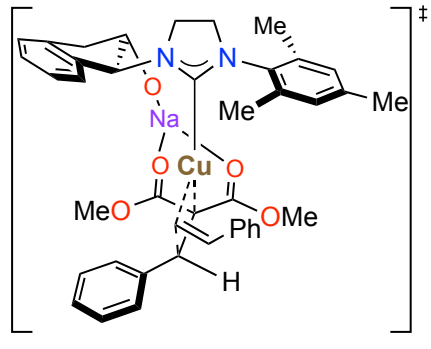


TS7

$\Delta\Delta H^{\ddagger} = 0.0$
$\Delta\Delta G^{\ddagger} = 0.0$



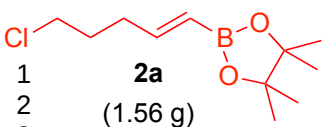
Disfavored



TS8

$\Delta\Delta H^{\ddagger} = 4.0$
$\Delta\Delta G^{\ddagger} = 2.2$

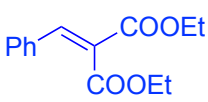
a



2a

(1.56 g)

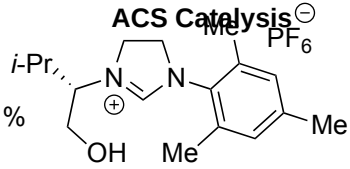
1.5 equiv.



1a

(1.12 g)

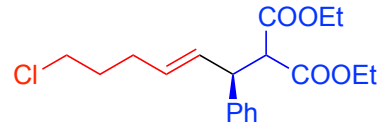
5.0 mol %



4f

5.0 mol % CuCl, 1.5 equiv. NaO*t*-Bu

THF, 22 °C, 16 h

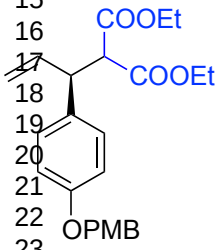


3a

(1.56 g)

98% yield, 95.5:4.5 e.r.

b

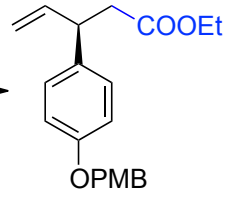


8d

96:4 e.r.

NaCl, DMSO, H_2O

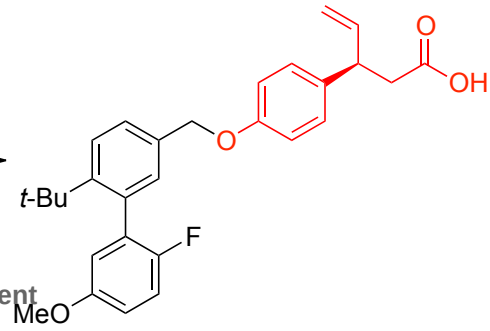
155 °C, 10 h



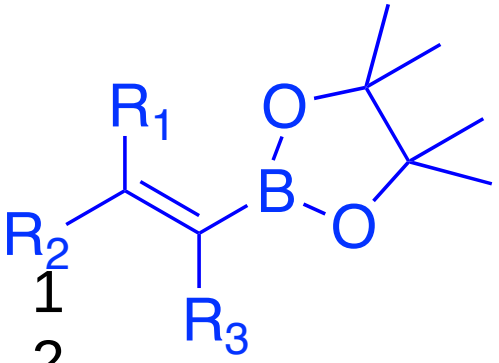
9

92% yield, 98:2 e.r.

ref 17



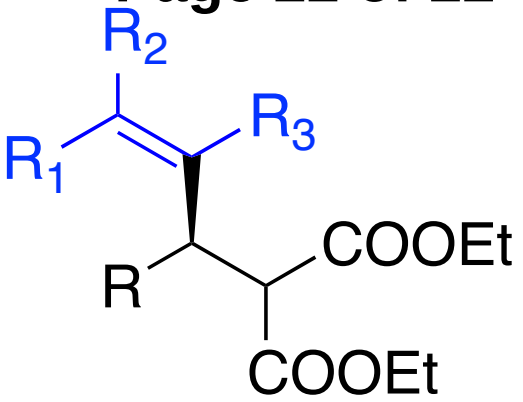
member of a family of GPR40 agonists



5–10 mol % NHC–Cu complex

1.5 equiv NaO*t*-Bu

THF, 22 °C, 16 h



ACS Paragon Plus Environment

28 examples

up to 98% yield

up to 99.5:0.5 e.r.