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Regioselective Carbonylation of 2,2-Disubstituted Epoxides: An Alternative Route to Ketone-Based Aldol Products

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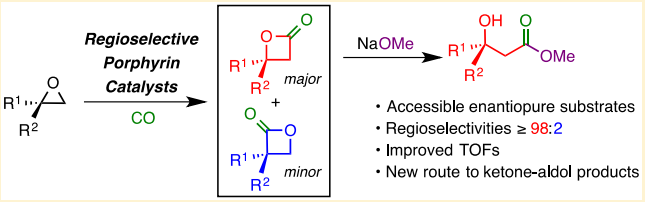
Supporting Information

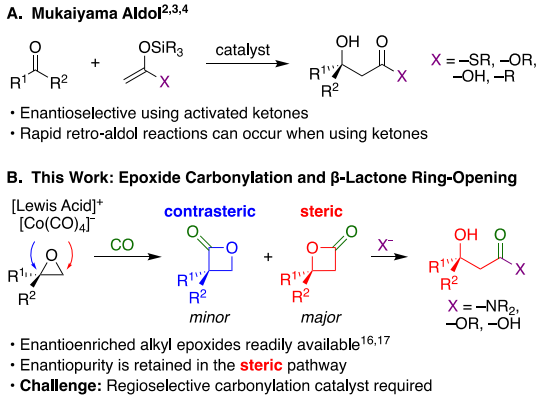
ABSTRACT: We report the regioselective carbonylation of 2,2-disubstituted epoxides to β,β-disubstituted β-lactones. Mechanistic studies revealed epoxide ring-opening as the turnover limiting step, an insight that facilitated the development of improved reaction conditions using weakly donating, ethereal solvents. A wide range of epoxides can be carbonylated to β-lactones, which are subsequently ring-opened to produce ketone-based aldol adducts, providing an alternative to the Mukaiyama aldol reaction. Enantiopure epoxides were demonstrated to undergo the carbonylation/ring-opening process with retention of stereochemistry to form enantiopure β-hydroxy esters.



INTRODUCTION

The aldol reaction[1] is one of the most widely used methods for carbon−carbon bond formation, both in nature and modern organic synthesis. While the stereoselective addition of an enolized carbonyl compound to an aldehyde has been well-established,[1] addition to ketones has proven particularly challenging.[2] This gap in the field is due to the inherent low reactivity and difficult enantiofacial discrimination of ketones, as well as the rapid retro-reactions of the products.[2] Significant progress[3] has been made since the introduction of the Mukaiyama aldol addition (Scheme 1A),[2−4] Reformatsky reaction,[5] and other similar transformations.[6] However, low temperatures, stoichiometric additives,[7,2d] and/or highly reactive α-dicarbonyl substrates are required to promote both reactivity and stereocontrol,[7,8] restricting the overall scope and practicality of these transformations. Despite these drawbacks, demand is high for ketone-aldol adducts, which have proven useful for the synthesis of chiral tertiary alcohols in natural products and pharmaceuticals.[4c,d,9] Thus, alternative synthetic methods are desired.

Scheme 1. (A) Mukaiyama Aldol Reaction and (B) Alternative Epoxide Carbonylation/Ring-Opening Route



Ketone-aldol products can also be synthesized via the cycloaddition of ketenes and ketones to produce β-lactones[10] that are subsequently ring-opened.[11] This method is often used in the synthesis of enantioenriched β-hydroxyacids,[10a,12] which are important due to their widespread use as enantiopure synthetic starting materials.[13] However, this procedure requires low reaction temperatures to prevent ketene dimerization and reaction with water, and few stereoselective processes have been reported.[14]

As an alternative to aldol and cycloaddition chemistries, we hypothesized that carbonylation techniques[15] could be applied to 2,2-disubstituted epoxides to produce a variety of β,β-disubstituted β-lactones. Kinetic resolutions[16] and enantioselective syntheses of 2,2-disubstituted epoxides[17] are established, providing a wide range of enantiopure starting materials. Because CO insertion typically occurs at the less-hindered carbon of the epoxide during carbonylation (*vide infra*), stereochemistry is retained. After carbonylation, these versatile β-lactone intermediates[18] can be ring-opened,[11d,e] providing a simple procedure for the generation of sought-after, enantioenriched ketone-aldol products (Scheme 1B).

In 1994, Drent and co-workers reported the first carbonylation of isobutylene oxide, the simplest 2,2-disubstituted epoxide, using a $Co_2(CO)_8$/3-hydroxypyridine catalyst.[19] This system produced the corresponding β,β-disubstituted β-lactone in 60% yield alongside various byproducts. The carbonylation of isobutylene oxide was not revisited until 2002 when our group reported a method[20] that afforded a 4:1 ratio of β,β-disubstituted to α,α-disubstituted β-lactone

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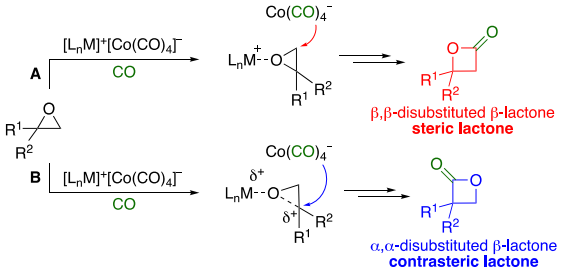
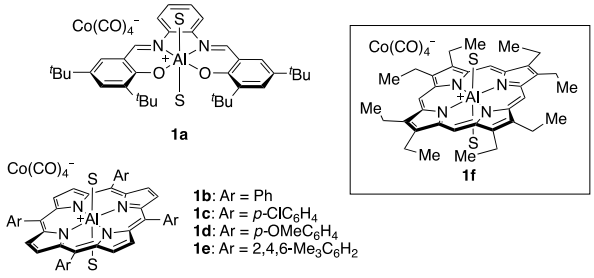
regioisomers, suggesting two possible reaction pathways. Epoxide ring-opening has traditionally been thought to occur via an S_N2 mechanism, wherein $Co(CO)_4^-$ attacks the least-hindered oxirane carbon to give the steric product (Scheme 2, pathway A). However, an S_N1-type mechanism could also occur to produce the contrasteric product (Scheme 2, pathway B); the disubstituted position allows formation of a stable tertiary carbocation or partial positive charge that enables attack at the more sterically congested site.[21]

Scheme 2. Steric and Contrasteric Ring-Opening for the Carbonylation of 2,2-Disubstituted Epoxides



In 2001, Alper and co-workers also observed the generation of two β-lactone regioisomers from propylene oxide and CO when using a $Co_2(CO)_8/BF_3{\cdot}OEt_2$ catalyst.[22] While this catalyst produced primarily the β-regioisomer, switching to $Co_2(CO)_8/B(C_6F_5)_3$ led to the formation of a significant amount of the α-product. Though the mechanism was not discussed, it is possible that the strongly Lewis acidic $B(C_6F_5)_3$ facilitated S_N1-type attack to yield the α-product. With this knowledge in hand along with our experience optimizing regioselective carbonylation reactions,[11d,e,23] we hypothesized that controlling the electronic properties of the [Lewis Acid]$^+$[$Co(CO)_4$]$^-$ catalysts (Chart 1) would be critical to achieve a highly regioselective, steric carbonylation of isobutylene oxide.

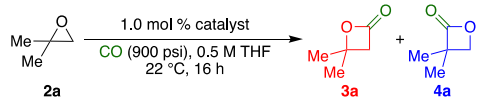
Chart 1. [Lewis Acid$(THF)_2$]$^+$[$Co(CO)_4$]$^-$ Catalysts Screened for Isobutylene Oxide Carbonylation (S = THF)



RESULTS AND DISCUSSION

Catalyst Optimization. Our first generation carbonylation catalyst [(salph)Al$(THF)_2$]$^+$[$Co(CO)_4$]$^-$ (**1a**) displayed low conversion and moderate regioselectivity for isobutylene oxide carbonylation at 22 °C (Table 1, entry 1). Although conversions improved using complexes **1b** and **1c** (Table 1, entries 2 and 3), regioselectivity remained modest (93:7). We therefore reduced the Lewis acidity to facilitate steric attack; however, introducing electron-donating *p*-OMe groups (**1d**, Table 1, entry 4) or mesityl rings (**1e**, Table 1, entry 5) decreased conversion with no change in regioselectivity. Next,

Table 1. Activity and Regioselectivity of Catalysts 1a−1f for the Carbonylation of Isobutylene Oxide



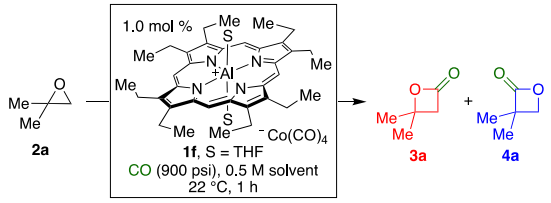
entry	catalyst	conv. (%)[a]	ratio 3a:4a[a]
1	**1a**	24	94:6
2	**1b**	>99	93:7
3	**1c**	97	93:7
4	**1d**	82	93:7
5	**1e**	62	93:7
6	**1f**	78	96:4

[a]Determined by ^{1}H NMR analysis of crude reaction mixture.

we screened an alkyl-substituted porphyrin (**1f**, Table 1, entry 6) to shift electron density onto the metal center. This octaethylporphyrin catalyst exhibited the highest regioselectivity (96:4) while maintaining good activity.

Mechanistic Investigations. In light of previous reports studying the effect of solvent donicity on carbonylation reactions, we performed a screen to further improve reaction rate and regioselectivity (Table 2).[24] Similar to these reports,

Table 2. Effect of Solvent on Activity and Regioselectivity



entry	solvent	TOF (h^{-1})[a,b]	ratio 3a:4a[a]
1	MeCN	0	nd[c]
2	THF	10	96:4
3	1,4-dioxane	10	95:5
4	DMTHF[d]	14	>99:1
5	Et_2O	14	99:1
6	$^iPr_2O$	17	>99:1
7	toluene	6	99:1
8	hexanes	3	94:6

[a]Determined by ^{1}H NMR analysis of crude reaction mixture. [b]TOF = turnover frequency = (mol starting material consumed)/[(mol catalyst)·(t_{rxn} in hours)]. [c]nd = not determined. [d]DMTHF = 2,5-dimethyltetrahydrofuran.

strongly donating acetonitrile (MeCN) coordinated to the catalyst, inhibiting epoxide binding and ultimately preventing reactivity (Table 2, entry 1). Reactions conducted in THF and 1,4-dioxane, common coordinating solvents, proceeded with a turnover frequency (TOF) of 10 h^{-1} and regioselectivities of 96:4 and 95:5, respectively (Table 2, entries 2 and 3). However, less donating ethers such as 2,5-dimethyltetrahydrofuran (DMTHF), diethyl ether (Et_2O), and diisopropyl ether ($^iPr_2O$) (Table 2, entries 4−6) facilitated faster reaction rates (TOF = 14−17 h^{-1}) and increased regioselectivities to >99:1. This increase in regioselectivity could be attributed to the solvents' inability to stabilize positive charge generated in the S_N1-type mechanism (Scheme 2, pathway B). Non-coordinating toluene and hexanes (Table 2, entries 7 and 8) did not shut down reactivity, but neither were competitive with

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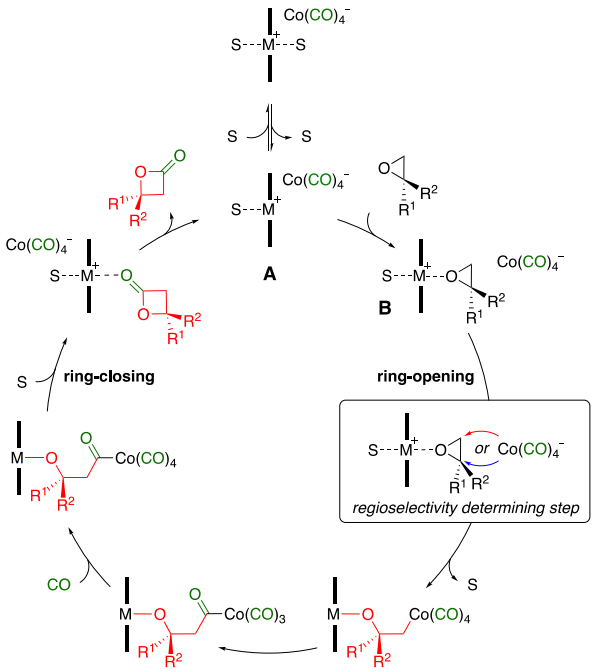
ethereal solvents. This decrease in activity indicates that a minimal amount of donicity is required for reaction turnover with weakly donating, ethereal solvents maximizing both TOF and regioselectivity.

Previous mechanistic studies using monosubstituted epoxides showed that strong donors, such as THF, are optimal because the turnover limiting step, ring closure, requires solvent coordination to the metal center (Scheme 3).[24] DMTHF, a weaker donor due to steric hindrance, slowed the carbonylation, supporting this mechanistic proposal.

Scheme 3. Proposed Mechanism for the Carbonylation of 2,2-Disubstituted Epoxides



However, in the case of 2,2-disubstituted epoxides, weakly donating solvents accelerated the reaction rate, prompting new mechanistic studies. To better understand this different trend, the reaction order in isobutylene oxide in both THF and $^{i}Pr_2O$ was determined (Figure 1). Unlike monosubstituted epoxides, which demonstrate a zero-order trend in epoxide using THF,[24]

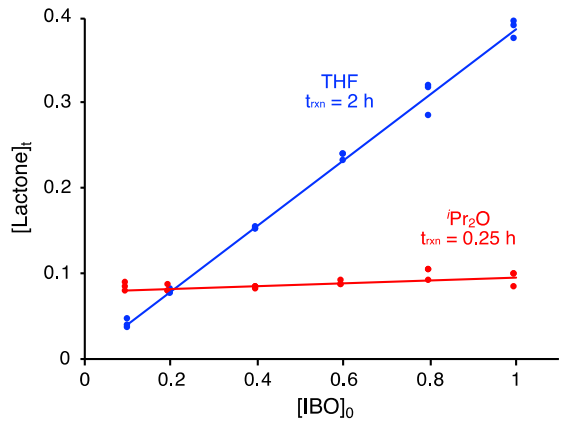


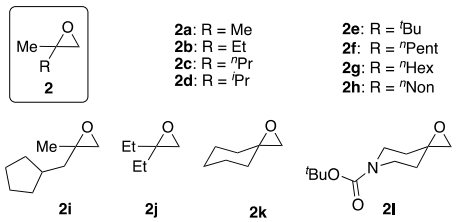
Figure 1. $[Lactone]_t$ dependence on $[IBO]_0$ (t_{rxn} = 2 h for THF and t_{rxn} = 0.25 h for $^{i}Pr_2O$) in different solvents using catalyst **1f**. IBO = Isobutylene oxide.

isobutylene oxide showed first-order behavior (Figure 1). We propose that this mechanistic difference is due to the addition of a second methyl group to the substituted carbon of the epoxide. This geminal dimethyl group likely facilitates ring closure via the Thorpe-Ingold effect,[25] ultimately changing the turnover limiting step from ring-closing to ring-opening in THF (Scheme 3).[16b]

This hypothesis is supported by the zero-order dependence on initial epoxide concentration in $^{i}Pr_2O$ (Figure 1). Because an axially bound solvent molecule dissociates during epoxide ring-opening, bulky and weakly coordinating solvents likely facilitate this step, implying the restoration of turnover limiting ring closure. However, we cannot rule out a change in catalyst resting state between unbound (Scheme 3, intermediate A) and bound epoxide (Scheme 3, intermediate B) with an accelerated turnover limiting ring-opening step. We also determined a first-order dependence on **1f** concentration, which is consistent with this mechanism. Less coordinating solvents such as toluene and hexanes likely exhibit decreased rates because ring closure still requires the binding of a solvent molecule.

Carbonylation Substrate Scope and Aldol Product Formation. Using these optimized conditions, alkyl 2,2-disubstituted epoxides (Chart 2) were carbonylated to afford

Chart 2. Scope of Alkyl 2,2-Disubstituted Epoxides



various β,β-disubstituted β-lactones with minimal side product formation (*vide infra*, **5**, Table 3). Substrates with a methyl group and an alkyl chain (Table 3, entries 1−8) were carbonylated in high yields and with ≥98:2 regioselectivity. Additional steric hindrance close to the epoxide substrate was also tolerated. Isopropyl and *tert*-butyl substitution (**2d** and **2e**, Table 3, entries 4 and 5) produced exclusively steric lactone in 79 and 70% isolated yield, respectively. Although regioselectivity was enhanced with increased steric bulk, the carbonylation reaction using **2e** was slow and required a higher catalyst loading to reach comparable conversion in the same amount of time. However, both regioselectivity and reaction rate remained high when the steric bulk was located one methylene unit farther from the quaternary center (**2i**, Table 3, entry 9). A substrate with two ethyl groups (**2j**, entry 10) as well as spirocyclic epoxides, **2k** and **2l**, were also carbonylated successfully (entries 11 and 12).

Each reaction exhibits an alkenyl decarboxylation side product (**5**, Table 3), which has been observed in similar transformations,[26] indicating a competing reaction pathway. Previous reports show evidence of a lactone [2 + 2] cycloreversion mechanism[27] that proceeds by way of a zwitterionic intermediate featuring a carboxylate and tertiary carbocation ($^{-}O_2CCH_2CR_2^{+}$).[27d] β-Substitution of the steric lactone (**3**) stabilizes the carbocation intermediate and facilitates the proposed pathway, but the contrasteric product cannot undergo the cycloreversion as it would require the formation of an unstable primary carbocation. This side

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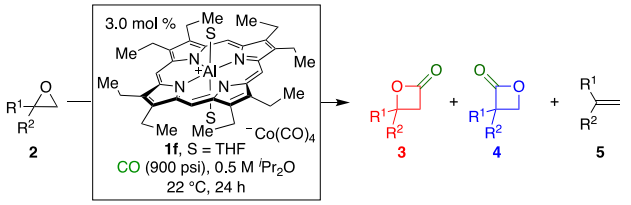
Table 3. Regioselective Carbonylation of Alkyl 2,2-Disubstituted Epoxides



entry	substrate	ratio 3:4[a]	isolated yield 3 (%)	alkene 5 (%)[a]
1	**2a**	98:2	78[b]	<1
2	**2b**	>99:1	51[b]	2
3	**2c**	98:2	66	<1
4	**2d**	>99:1	79	2
5[c]	**2e**	>99:1	70	<1
6	**2f**	98:2	79	2
7	**2g**	98:2	88	2
8	**2h**	98:2	46	3
9	**2i**	98:2	78	2
10	**2j**	>99:1	47[b]	3
11	**2k**	99:1	67	<1
12	**2l**	>99:1	91	3

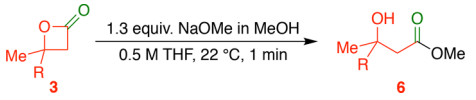
[a]Determined by ^{1}H NMR analysis of crude reaction mixture. [b]NMR yield versus hexamethyldisiloxane as an internal standard. [c]5.0 mol % of **1f**.

reaction is avoided by stopping the reactions immediately after, or just before, full conversion is reached.

Other 2,2-disubstituted epoxides did not require **1f** to achieve high regioselectivities, so the cheaper and more easily synthesized catalyst **1b** was used instead (Table 4). Epoxides **2m**, **2n**, and **2o**, which contain aromatic substituents (Table 4, entries 1−3), were carbonylated in moderate yield and excellent regioselectivity. A methyl-substituted analogue of epichlorohydrin (**2p**, Table 4, entry 4) produced exclusively steric lactone in 84% isolated yield, and substrates with TBS-protected alcohols (**2q** and **2r**, Table 4, entries 5 and 6) were also carbonylated efficiently. Methacrylate-derived substrates **2s** and **2t** (Table 4, entries 7 and 8) required higher temperatures and longer reaction times, but regioselectivity remained impressive.

The class of alkyl-substituted lactones represented in Tables 3 and 4 are of particular importance since many aldol reactions using alkyl ketones suffer from low stereoselectivities.[2,4,7,8] On the basis of a previously reported carbonylation/ring-opening procedure,[11d,e,23] a variety of alkyl, ketone-aldol-type products were generated in near quantitative yields (Table 5). Epoxides

Table 5. Mukaiyama-Type Aldol Products Formed via the Methanolysis of *β*-Lactones



entry	*β*-lactone	R	product	isolated yield 6 (%)[a]
1	**3f**	^{n}Pent	**6f**	91
2	**3m**	Bn	**6m**	98
3	**3n**	CH_2Bn	**6n**	90
4	**3o**	CH_2OPh	**6o**	96
5	**3r**	CH_2CH_2OTBS	**6r**	98
6	**3t**	$CO_2{}^tBu$	**6t**	85

[a]See the Supporting Information for more details.

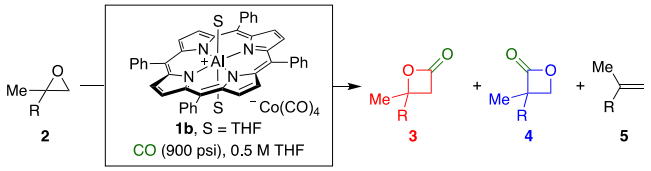
were subjected to the corresponding carbonylation conditions shown in Tables 3 and 4 and purified before the addition of sodium methoxide in methanol. With kinetic resolutions that guarantee >99:1 e.r.,[16] this method is complementary to recent advances in Mukaiyama aldol chemistry,[3] which highlight a number of aryl and alkenyl products.

To test whether enantiopurity is maintained through our carbonylation and methanolysis procedures, enantiopure substrates (*R*)-**2n** and (*R*)-**2r** were synthesized in >99:1 e.r. using a kinetic resolution developed by Jacobsen and co-workers[16c,d] (Scheme 4). The corresponding lactone products were synthesized in >99:1 e.r. without loss of enantiopurity and with complete retention of stereochemistry before subsequent methanolysis.

CONCLUSION

We have developed a highly efficient and regioselective process for the carbonylation of 2,2-disubstituted epoxides using an octaethylporphyrin catalyst, **1f**, and a tetraphenylporphyrin catalyst, **1b**. Mechanistic experiments revealed that the

Table 4. Regioselective Carbonylation of Challenging 2,2-Disubstituted Epoxides Using Catalyst 1b



entry	substrate	R	mol % catalyst	temp (°C)	time (h)	ratio 3:4[a]	isolated yield 3 (%)	alkene 5 (%)[a]
1	**2m**	Bn	2	60	6	98:2	67	2
2	**2n**	CH_2Bn	3	60	8	99:1	51	<1
3	**2o**	CH_2OPh	3	60	8	>99:1	81	<1
4	**2p**	CH_2Cl	3	40	4	>99:1	84	<1
5	**2q**	CH_2OTBS[b]	4	40	5	99:1	99	<1
6	**2r**	CH_2CH_2OTBS[b]	3	40	5	96:4	91	4
7	**2s**	CO_2Me	2	60	18	98:2	83	<1
8	**2t**	$CO_2{}^tBu$	3	60	28	98:2	58	<1

[a]Determined by ^{1}H NMR analysis of crude reaction mixture. [b]TBS = ^{t}BuMe$_2$Si

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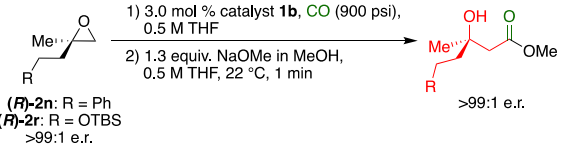
Scheme 4. Stereochemistry of Carbonylation and Ring-Opening Steps



turnover limiting step is epoxide ring-opening, an insight that facilitated the development of a faster system using weakly donating, ethereal solvents. With optimized reaction conditions in hand, a large range of alkyl epoxides was carbonylated regioselectively. These epoxide substrates can be prepared in enantiopure form to produce enantiopure ketone-aldol-type products traditionally accessed via Mukaiyama aldol reactions. This sought-after tertiary alcohol functionality remains an important component of various natural products and pharmaceuticals.[4c,d,9] To the best of our knowledge, this is the first report of a carbonylative approach to the production of difficult-to-access ketone-aldol products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b12286.

Synthetic procedures, characterization data of all new compounds, control reactions, and expanded additional mechanistic data (PDF)

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Notes

The authors declare no competing financial interest.

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