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Chemo- and Stereoselective Cross Rauhut-Currier-Type Reaction of Tri-substituted Alkenes Containing Trifluoromethyl Groups

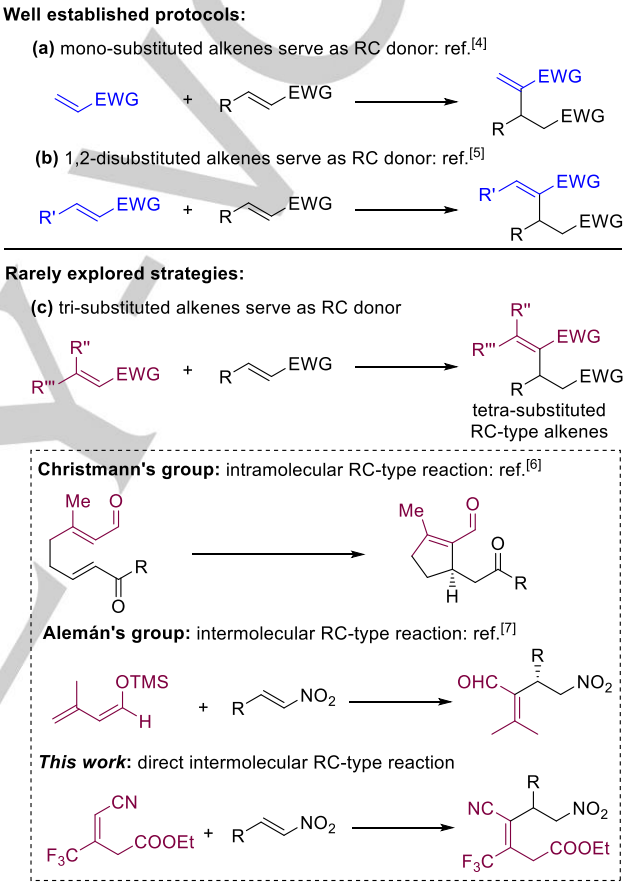
Xiang-Hong He, Lei Yang, Yan-Ling Ji, Qian Zhao, Ming-Cheng Yang, Wei Huang, Cheng Peng* and Bo Han*

Dedication ((optional))

Abstract: A chemoselective cross Rauhut-Currier-type reaction has been developed involving a tri-substituted alkene (trifluoromethyl-containing acrylonitrile derivative) with a di- or tri-substituted alkene to yield tetra-substituted double bonds in RC-type products. This approach can support the synthesis of trifluoromethylated tetra-substituted olefins and synthetically important, structurally complex 3-allylic-type oxindole skeletons. The asymmetric version of this RC-type reaction can be realized by combining a Brønsted acid and Lewis base for bifunctional H-bonding-tertiary amine catalysis. Subsequent transformation of multi-functionalized RC-type product leads to pharmacologically interesting cyclohexane-based spiro-pyrazolones bearing six contiguous chiral centers and two highly congested, vicinal quaternary carbon centers.

Introduction

The Rauhut-Currier (RC) reaction, first described by Rauhut and Currier in 1963 and also known as the vinylogous Morita-Baylis-Hillman reaction,[1] is an efficient, atom-economic approach to multi-substituted alkenes. This powerful method for forming C-C bonds has been applied to the synthesis of several biologically important targets and natural products.[2] Much more challenging is the so-called “cross Rauhut-Currier” reaction between two different activated alkenes, which normally proceeds with poor selectivity.[3] Cross RC reactions have been extensively explored between a mono-substituted alkene and another electron-deficient alkene (Scheme 1a),[4] as well as between a 1,2-disubstituted alkene and another electron-deficient alkene (Scheme 1b).[5] Previous studies have demonstrated that 1,2,2-tri-substituted alkenes are poor donors in cross RC reactions, likely because of steric hindrance, which means that few methods exist to generate tetra-substituted RC-type products (Scheme 1c).[6,7] In 2009, Christmann and co-workers generated RC-type products with a tetra-substituted alkene via dienamine-activated intramolecular enantioselective Michael/isomerization



Scheme 1. The Application of RC Reaction in Building Multi-substituted Alkenes

cyclization of 1,2,2-tri-substituted alkenes and α,β-unsaturated aldehydes in the presence of secondary amine catalyst.[6] More recently, Alemán’s group generated tetra-substituted RC-type products via intermolecular regioselective Mukaiyama reaction in the presence of bifunctional catalyst.[7] While these advances are important, many types of tetra-substituted RC-type products remain inaccessible.

Trifluoromethyl (CF_3) is a privileged structural motif playing a crucial role in many drugs,[8] so organic chemists continue to spend considerable efforts on constructing CF_3-containing organic compounds.[9] Trifluoromethylated alkenes,[10] especially 3,3,3-trifluoropropene derivatives, are particularly attractive

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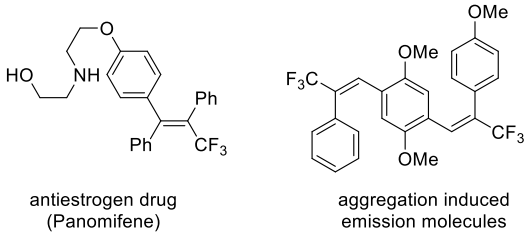
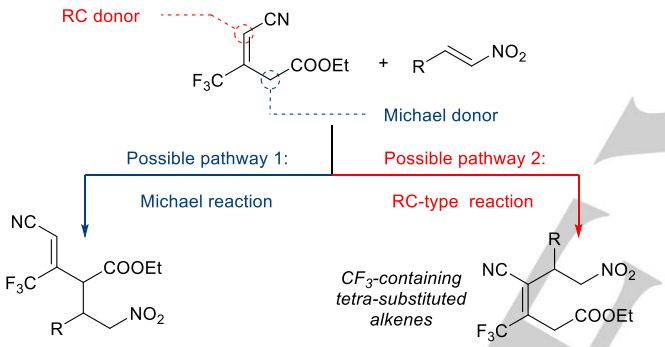


Figure 1. Representative examples of multisubstituted CF_3-alkenes.

organic skeletons because of their significant usefulness as pharmaceuticals or functional molecules (Figure 1).[11]

For the foregoing reasons, coupled with our own recent success developing organocatalytic reactions to assemble synthetically important and structurally complex molecules,[12] we have designed a novel multi-functionalized CF_3-alkene **1a** with two different reactive sites, which we hypothesized could serve as a Michael donor or as an RC donor *via* the strong electron withdrawing groups on the substrate (Scheme 2).

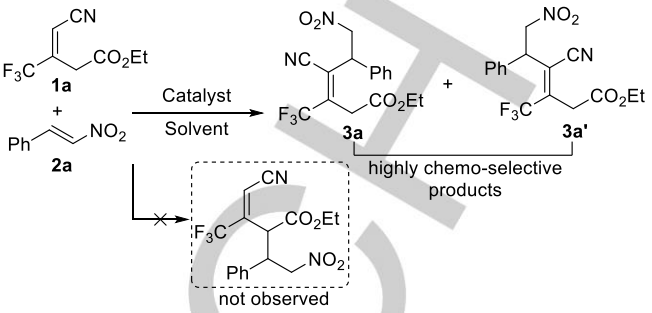


Scheme 2. Synthetic strategy.

Results and Discussion

We probed the reactivity and selectivity of ethyl (*E*)-4-cyano-3-(trifluoromethyl)-but-3-enoate **1a** by reacting it initially with nitrostyrene **2a** in dichloromethane at room temperature for 3 h in the presence of 20 mol% trimethylamine. We were pleased to obtain exclusively the RC-type product in 75% yield with a moderate *Z/E* ratio of 82:18 (Table 1, entry 1). Next, we optimized the reaction by screening additional parameters in the presence of trimethylamine (Table 1). Various solvents supported the reaction, allowing formation of the desired RC-type product (entries 1-4), with dichloromethane showing the highest efficiency (entry 1). Raising the reaction temperature substantially improved the reaction rate but significantly decreased yield and *Z/E* ratio (entry 5), while lowering the temperature decreased the reaction rate without improving yield or *Z/E* ratio (entry 6). Using the relatively strong base catalysts DIPEA and DBU supported rapid reaction but at a cost of lower yield and *Z/E* ratio (entries 7-8). Using the weak base catalysts

Table 1. Optimization of reaction conditions.[a]

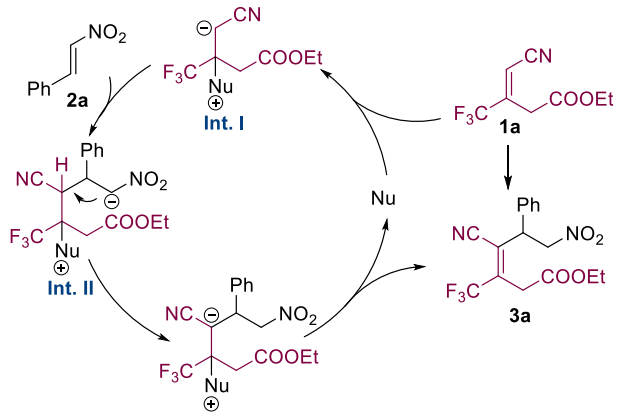


Entry	Solvent	Catalyst	Time [h][b]	Yield [%][c]	*Z/E* [**3a**:**3a'**][d]
1	CH_2Cl_2	TEA	3	75	82:18
2	Toluene	TEA	2	64	69:31
3	MeCN	TEA	4	57	78:22
4	THF	TEA	6	46	60:40
5[e]	CH_2Cl_2	TEA	1	37	63:37
6[f]	CH_2Cl_2	TEA	6	65	74:26
7	CH_2Cl_2	DIPEA	0.5	54	67:23
8	CH_2Cl_2	DBU	0.5	28	55:45
9	CH_2Cl_2	DABCO	4	75	81:19
10	CH_2Cl_2	DMAP	4	68	73:27
11	CH_2Cl_2	PPh_3	6	79	90:10

[a] Unless noted otherwise, reactions were performed with 0.30 mmol of **1a**, 0.20 mmol of **2a**, and 0.04 mmol of base catalyst in 1 mL of solvent at room temperature. For the relative configuration of **3a** and **3a'**, see entry 9 in Table 2. [b] Indicates the time after which total yield of **3a** and **3a'** did not increase. [c] Total yield of isolated **3a** and **3a'**. [d] Calculated based on ^{1}H NMR analysis of the crude reaction mixture. [e] Reaction performed at 50 °C. [f] Reaction performed at 0 °C.

DABCO and DMAP led to slower reaction but better yield and *Z/E* ratio (entries 9-10). Interestingly, using the traditional nucleophilic reagent PPh_3 as base catalyst led to good yield and *Z/E* ratio (entry 11).

Under optimal reaction conditions, various alkaline or nucleophilic catalysts promoted the reaction (Table 1). We postulate two reaction pathways that could explain the highly chemoselective RC-type products observed (Scheme 3). The more likely reaction pathway is a traditional RC reaction in the presence of nucleophilic reagent (path *a*). Another possible pathway is a complicated deprotonation-isomerization-Michael-isomerization cascade (path *b*). When we conducted the reaction using PPh_3 or DABCO (entries 9 and 11), which are poor bases but good nucleophiles, ESI-MS revealed the presence of intermediates consistent with path *a*.[13] On the other hand, conducting the reaction with the weakly nucleophilic base DIPEA (entry 7) accelerated the reaction to afford the desired

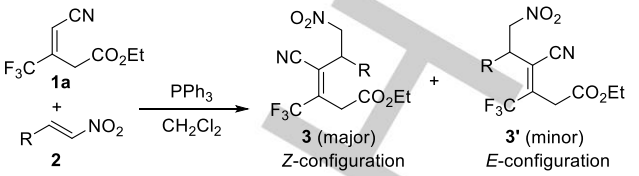


Scheme 3. Proposed catalytic cycle to yield the RC-type product with high selectivity.

product, which is consistent with path *b*. We conclude that the reaction probably proceeds *via* an RC pathway, but we cannot exclude the possibility that it also proceeds *via* a Michael cascade at least under certain conditions.

Having established the optimal conditions (Table 1, entry 11), we examined the scope of the reaction. Substrates with nearly any substitution at the *ortho*-, *meta*-, or *para*-position on the aromatic groups of nitroolefin **2** gave the desired products in moderate to good yields and high *Z/E* ratios (Table 2, entries 2-18). Higher yields and *Z/E* ratios were obtained when the nitroolefin **2** bearing electron-donating groups (entries 3-9) rather than electron-neutral or -withdrawing groups (entries 1 and 11-18). Substitutions at the *ortho*-position of nitroolefin led to relatively inefficient reaction (entries 2 and 10), perhaps as a result of steric hindrance. Heteroaryl nitroolefin gave the target product **3s**, albeit in slightly lower yield (entry 19). Naphthaldehyde nitroolefin also afforded the corresponding products in good yields and with moderate to high *Z/E* ratios (entries 20 and 21).

Table 2. Substrate scope of the RC-type reaction.[a]



Entry	R	Time [h][b]	Product	Yield [%][c]	*Z/E* [3:3']][d]
1	Ph	6	**3a/3a'**	79	90:10
2	2-$CH_3C_6H_4$	8	**3b/3b'**	72	>95:5
3	3-$CH_3C_6H_4$	7	**3c/3c'**	83	>95:5
4	4-$CH_3C_6H_4$	7	**3d/3d'**	81	>95:5
5	3-$OMeC_6H_4$	7	**3e/3e'**	85	>95:5
6	4-$OMeC_6H_4$	7	**3f/3f'**	83	>95:5
7	4-*t*-BuC_6H_4	7	**3g/3g'**	84	>95:5
8	4-*i*-PrC_6H_4	7	**3h/3h'**	82	>95:5
9	3,4-$(OMe)_2C_6H_3$	8	**3i**[e]**/3i'**[f]	87	92:8
10	2-FC_6H_4	5	**3j/3j'**	68	>95:5
11	3-FC_6H_4	5	**3k/3k'**	76	>95:5
12	4-FC_6H_4	5	**3l/3l'**	78	>95:5
13	3-ClC_6H_4	5	**3m/3m'**	80	>95:5
14	4-ClC_6H_4	5	**3n/3n'**	74	>95:5
15	3-BrC_6H_4	5	**3o/3o'**	76	91:9
16	4-BrC_6H_4	5	**3p/3p'**	75	86:14
17	4-$NO_2C_6H_4$	2	**3q/3q'**	64	>95:5
18	3,4-$Cl_2C_6H_3$	4	**3r/3r'**	71	>95:5
19	2-thienyl	5	**3s/3s'**	57	>95:5
20	α-naphthyl	6	**3t/3t'**	79	88:12
21	β-naphthyl	6	**3u/3u'**	83	>95:5

[a] See entry 11 and footnote a in Table 1. [b] Indicates the time after which total yield of **3** and **3'** did not increase. [c] Total yield of isolated **3** and **3'**. [d] Calculated based on ^{1}H NMR analysis of the crude reaction mixture. [e] The relative configuration of compound **3i** was confirmed by X-ray crystallographic analysis (Figure 2),[14] and the relative configurations of other products **3** were tentatively assigned by analogy. [f] The relative configuration of compound **3i'** was confirmed by X-ray crystallographic analysis (Figure 2),[15] and the relative configurations of other products **3'** were tentatively assigned by analogy.

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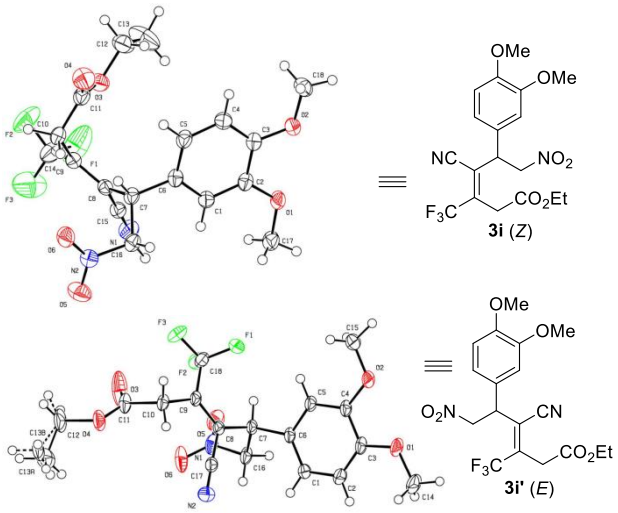
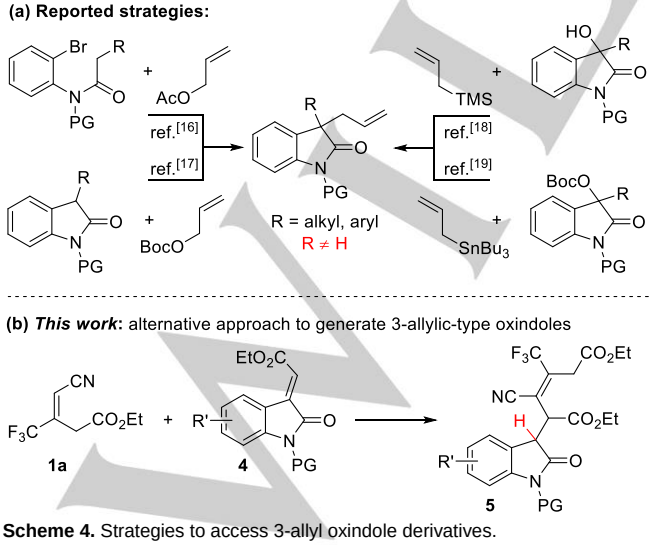


Figure 2. ORTEP drawing of compounds **3i** and **3i'**. Ellipsoids are shown at the 50% probability level.

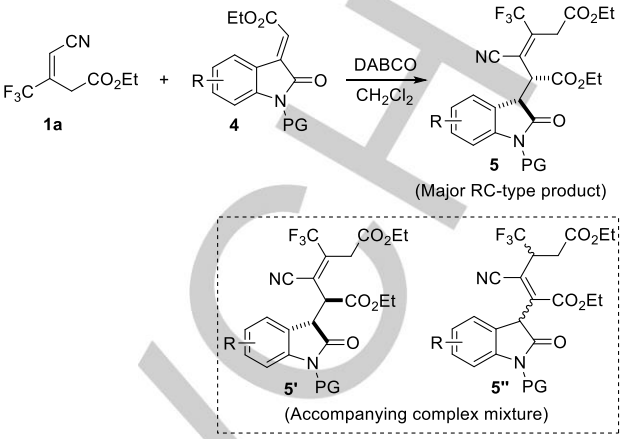
Subsequently, we attempted to use a 1,2,2-tri-substituted alkene as RC-type acceptor. Our goal was to determine whether such a substrate could complement traditional strategies (Scheme 4a)[16-19] to efficiently generate a multi-functionalized 3-allylic-type oxindole derivatives (Scheme 4b). Such a skeleton is an important synthon used to prepare many natural products or pharmaceutical lead compounds.[20]

We began our studies using the potential RC-type acceptor 3-ylideneoxindole **4**. The base catalyst PPh_3 did not lead to satisfactory results, while tertiary amines, especially DABCO, promoted the reaction smoothly to afford a major RC-type product together with minor complex by-products, which likely contain the diastereoisomer, *Z*/*E*-isomers and double-bond migration products of **5**. Meanwhile we explored whether the reaction would tolerate substitutions on the oxindole core of the major RC-type product. Changing the functional group on the R



Scheme 4. Strategies to access 3-allyl oxindole derivatives.

Table 3. Extensive substrate scope of the RC-type reaction.[a]



Entry	R	PG	Time [h][b]	Product	Yield [%][c]
1	H	Bn	1	**5a**	69
2	5-Cl	Bn	1	**5b**[d]	61
3	5-Br	Bn	1	**5c**	64
4	7-F	Bn	1	**5d**	67
5	5-Me	Bn	2	**5e**	71
6	H	Me	1	**5f**	42
7	H	Allyl	1	**5g**	47

[a] Unless noted otherwise, reactions were performed with 0.30 mmol of **1a**, 0.20 mmol of **4**, and 0.04 mmol of DABCO in 1 mL CH_2Cl_2 at 0 °C. [b] Indicates the time after which yield of **5** did not increase. [c] Yield of isolated major product **5**. [d] The relative configuration of compound **5b** was confirmed by X-ray crystallographic analysis (Figure 3),[21] and the relative configurations of other products **5** were tentatively assigned by analogy.

of the oxindole core slightly affected the reaction, particularly halides (Table 3, entries 1-5). The reaction did not tolerate a Boc group but it did tolerate methyl and allyl groups, although yields were substantially lower (Table 3, entries 6 and 7). Unfortunately, we failed to purify the target products of these reactions from the complex by-products. Nevertheless, we did manage to isolate a small amount of double-bond migration products **5a''** and **5e''** obtained when the R group was H or 5-Me, respectively (see NMR and HRMS spectra in Electronic Supplementary Information).

To explore the reaction scope further, we tested the ability of phenyl-substituted alkene **1b** to serve as an RC donor. PPh_3 failed to catalyze this reaction, so we screened the base catalysts DBU, DIPEA, DABCO, DMAP and TEA. DABCO led to the most efficient reaction, which generated the conventional Michael addition product **6a** rather than the predicted RC-type product (Scheme 5). This result indicates that the CF_3 group is essential for obtaining highly chemoselective RC-type products in our reaction.

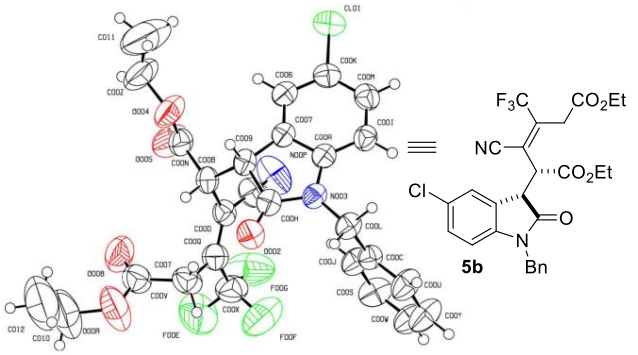
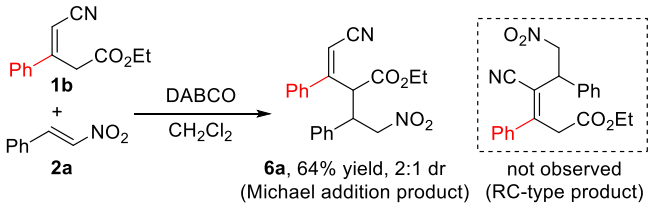


Figure 3. ORTEP drawing of compound **5b**. Ellipsoids are shown at the 50% probability level.



Scheme 5. The Michael addition reaction between phenyl substituted alkene 1b and nitroolefin 2a.

To extend the synthetic usefulness of our RC-type approach, we attempted to achieve the asymmetric version in the presence of an appropriate organocatalyst.[22] We also focused on exploring the unusual activation modes of bifunctional hydrogen-bonding-tertiary amine organocatalysis because of our continuing efforts to expand the repertoire of organocatalytic tools.[23] For the same reason, instead of the more common bifunctional catalytic strategy of combining a Brønsted acid with a Brønsted base (Figure 4, *left*),[24] we planned to combine a Brønsted acid and Lewis base (Figure 4, *right*) on the basis of recent success using a Brønsted acid and neutral coordinate bifunctional organocatalyst (Figure 4, *middle*).[7]

We attempted the asymmetric version of our reaction in the presence of numerous chiral catalysts (Table 4). The *Cinchona* alkaloids quinine (**C1**), cinchonine (**C2**) and β-isocupreidine (β-ICD, **C3**) provided the desired product in good yield but with poor enantioselectivity (entries 1-3). Various kinds of bifunctional catalysts were also tested, including Takemoto's catalysts (**C4**, **C5**), thiourea-based tertiary amine derivatives (**C6**, **C7**), and squaramide-based *cinchona* alkaloid derivative **(C8)**. Nevertheless, only poor to moderate *ee* values were obtained (entries 4-8), with alkaloid catalyst **C8** providing the best results of 72% yield and 83% *ee* (entry 8). Combining bisthiourea catalyst **C9** with alkaloids **C1** or **C8** did not improve enantioselectivity (entries 9-10), nor did stereoselectivity improve with different solvents (entries 11-14), reaction temperatures or catalyst loadings (entries 15-17).

We propose that the asymmetric RC-type reaction in the case of the most powerful bifunctional H-bonding-tertiary amine catalyst involves the transition state shown in Figure 5**,** reflecting a possible Brønsted acid-Lewis base activation mode. ESI-MS analysis of reaction mixtures revealed intermediates of catalyst **C8** predicted by our catalytic cycle.[25] However, as mentioned above, we cannot totally repudiate the possibility that it also proceeds *via* a catalytic strategy combining a Brønsted acid with a Brønsted base.

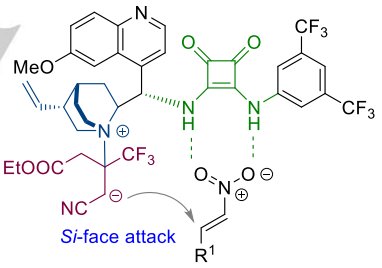


Figure 5. The proposed transition state of a Brønsted acid-Lewis base activation mode.

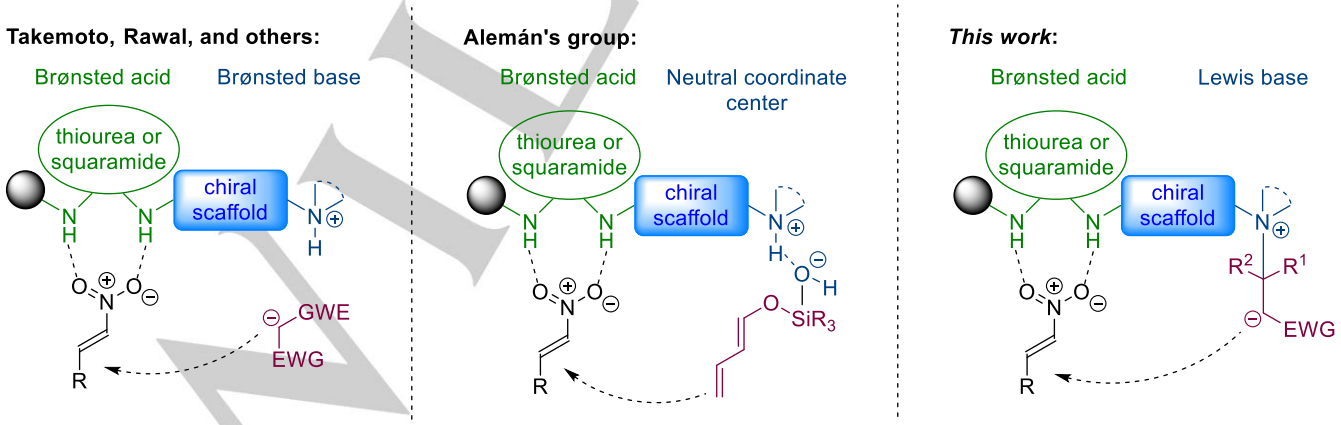
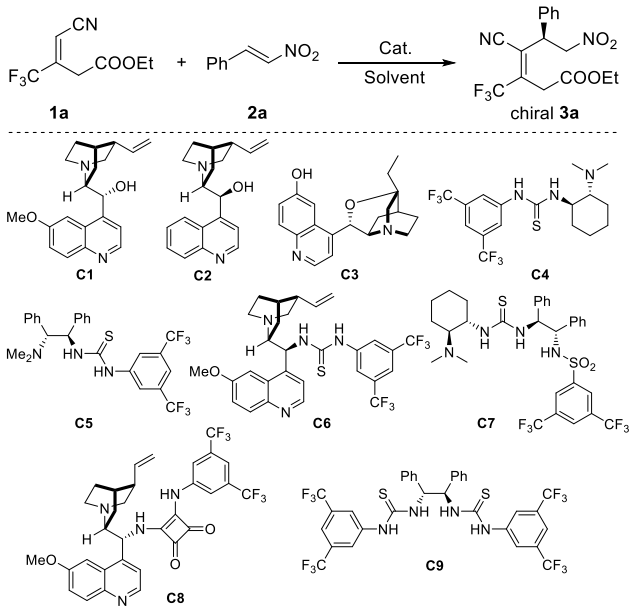


Figure 4. Three activation modes of bifunctional H-bonding-tertiary amine catalysts.

Table 4. Optimization of conditions for the asymmetric RC-type reaction.[a]



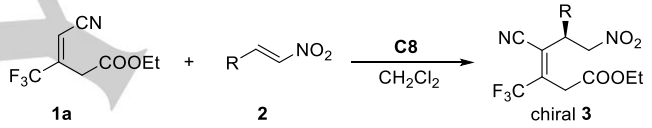
Entry	Cat.	Solvent	Time [h][b]	Yield [%][c]	*Z*/*E* [**3a**:**3a'**][d]	*ee* [%][e]
1	**C1**	CH_2Cl_2	4	76	>95:5	41
2	**C2**	CH_2Cl_2	4	73	>95:5	29
3	**C3**	CH_2Cl_2	12	62	>95:5	65
4	**C4**	CH_2Cl_2	6	65	>95:5	44
5	**C5**	CH_2Cl_2	8	62	>95:5	51
6	**C6**	CH_2Cl_2	12	70	>95:5	41
7	**C7**	CH_2Cl_2	12	68	>95:5	-45
8	**C8**	CH_2Cl_2	8	72	>95:5	83
9[f]	**C9**+**C1**	CH_2Cl_2	6	74	>95:5	53
10[g]	**C9**+**C8**	CH_2Cl_2	10	70	>95:5	76
11	**C8**	Toluene	8	68	>95:5	67
12	**C8**	MeCN	8	65	>95:5	64
13	**C8**	THF	10	56	>95:5	55
14	**C8**	$CHCl_3$	10	67	>95:5	79
15[h]	**C8**	CH_2Cl_2	24	64	>95:5	81
16[i]	**C8**	CH_2Cl_2	36	53	>95:5	80
17[j]	**C8**	CH_2Cl_2	4	69	>95:5	82

[a] Unless noted otherwise, reactions were performed with 0.30 mmol of **1a**, 0.20 mmol of **2a**, and 0.04 mmol of chiral catalyst in 1 mL of solvent at room temperature. [b] Indicates the time after which yield of chiral **3a** did not increase. [c] Yield of isolated chiral **3a**. [d] Calculated based on ^{1}H NMR analysis of the crude reaction mixture. [e] Determined by HPLC using a chiral stationary phase. [f] 0.02 mmol of **C9** and 0.02 mmol of **C1** were used. [g] 0.02 mmol of **C9** and 0.02 mmol of **C8** were used. [h] Reaction performed at 0 °C. [i] Reaction performed at -20 °C. [j] 0.08 mmol of **C8** was used.

Using optimized reaction conditions (Table 4, entry 8), we succeeded in generating typical asymmetric RC-type products in good yields and with excellent *Z*/*E* ratios (Table 5). Enantioselectivity was greater when the nitroolefin **2** carried electron-donating groups (entries 3-6) than when it carried electron-withdrawing groups (entries 8-10). Enantioselectivity up to 91% *ee* was obtained with nitroolefin **2** bearing a methoxy group (entries 3, 4 and 6). Slightly lower enantioselectivity was obtained when the nitroolefin was substituted at the ortho-position (entries 2 and 7), perhaps as a result of steric hindrance. Heteroaryl nitroolefin gave the target product **3s,** albeit in slightly lower yield and poorer *ee* (entry 11). Naphthaldehyde nitroolefin afforded the corresponding products in good yield but with poor enantioselectivity (entry 12). Using 3-alkenyl-substituted oxindole **4a**, a tri-substituted alkene, instead of nitroolefin **2** led to lower enantioselectivity,[26] probably because **4a** lacks the hydrogen bond-accepting nitro group.

The synthetic usefulness of our RC-type reaction lies in its ability to generate a tetra-substituted alkene containing an activated methylene group and an activated alkene. This

Table 5. Substrate scope of the asymmetric RC-type reaction.[a]



Entry	R	Time [h][b]	Product	Yield [%][c]	*Z*/*E* [**3:3'**][d]	*ee* [%][e]
1	Ph	8	chiral **3a**	72	>95:5	83
2	2-$CH_3C_6H_4$	12	chiral **3b**	73	>95:5	75
3	3-$OMeC_6H_4$	12	chiral **3e**	75	>95:5	87
4	4-$OMeC_6H_4$	12	chiral **3f**	77	>95:5	88
5	4-*i*-PrC_6H_4	12	chiral **3h**	76	>95:5	83
6	3,4-$(OMe)_2C_6H_3$	12	chiral **3i**	78	>95:5	91
7	2-FC_6H_4	6	chiral **3j**	57	>95:5	72
8	3-ClC_6H_4	6	chiral **3m**	65	>95:5	82
9	4-BrC_6H_4	6	chiral **3p**	69	>95:5	82
10	3,4-$Cl_2C_6H_3$	6	chiral **3r**	64	>95:5	83
11	2-thienyl	8	chiral **3s**	60	>95:5	77
12	β-naphthyl	8	chiral **3u**	67	>95:5	56

[a] See entry 8 and footnote a in Table 3. [b] Indicates the time after which the yield of 3 did not increase. [c] Yield of isolated chiral 3. [d] Calculated based on ^{1}H NMR analysis of the crude reaction mixture. [e] Determined by HPLC using a chiral stationary phase.

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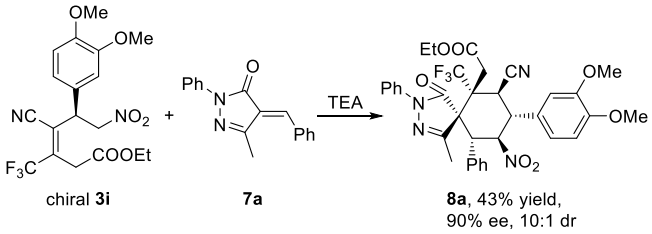

Scheme 6. Asymmetric synthesis of fully substituted cyclohexane-based spiropyrazolone.

species can serve as a 1,4-synthon in a [4+2] cyclization reaction to provide cyclohexane-fused drug-like scaffolds. To illustrate this synthetic potential, we reacted this tetra-substituted alkene **3i** with pharmacologically interesting pyrazolone[27] **7a** in the presence of 20 mol% trimethylamine in dichloromethane at room temperature (Scheme 6). To our delight, we obtained a spirocyclohexane-based pyrazolone[28] **8a** containing six contiguous chiral centers and two highly congested, vicinal quaternary stereocenters in 43% yield and 90% *ee*.

The absolute configuration of **8a** was determined by X-ray crystallographic analysis (Figure 6),[29] and from this we also tentatively inferred the absolute configuration of chiral **3i**. The absolute configurations of the other chiral RC-type products **3** were tentatively assigned by analogy.

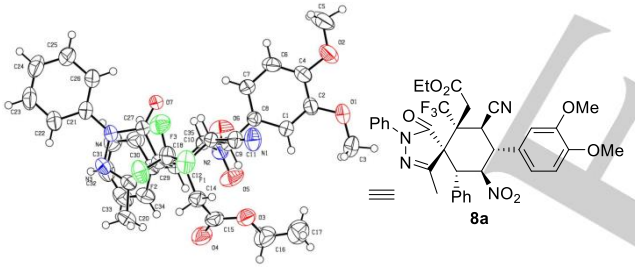

Figure 6. ORTEP drawing of compound **8a**. Ellipsoids are shown at the 50% probability level.

Conclusions

In conclusion, we have presented an efficient chemo- and regio-selective cross RC-type reaction in which a tri-substituted alkene serves as an RC-type donor. Using this strategy, we easily obtained multi-functionalized, tetra-substituted RC-type products. Both 1,2-disubstituted and 1,2,2-trisubstituted alkenes participated as RC-type acceptors in the reaction. When 3-ylidene oxindole was employed as RC-type acceptor, we obtained a 3-allylic-type oxindole skeleton, widely used in the synthesis of various natural products or pharmaceutical lead compounds. We also achieved the asymmetric version of this RC-type reaction using the possible combination of a Brønsted acid and Lewis base, extending the applications of bifunctional H-bonding-tertiary amine organocatalysts. More interestingly, the RC-type products served as 1,4-synthons in [4+2] cyclization to provide elegant access to fully substituted spirocyclohexane-based pyrazolones bearing two highly congested contiguous quaternary carbon centers.

Experimental Section

General Methods. NMR data were obtained for ^{1}H at 400 MHz or 600 MHz, and for ^{13}C at 100 MHz or 150 MHz. Chemical shifts were reported in ppm from tetramethylsilane using solvent resonance in $CDCl_3$ solution as the internal standard. ESI HRMS was performed on a Waters SYNAPT G2. Enantiomeric ratios were determined by comparing HPLC analysis of products on chiral columns with results obtained using authentic racemates. The following Daicel Chiralpak columns were used: AS-H (250 x 4.6 mm), AD-H (250 x 4.6 mm), IC (250 x 4.6 mm) or IE (250 x 4.6 mm). UV detection was performed at 220 nm or 254 nm. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at 20 °C. Column chromatography was performed on silica gel (200-300 mesh) using an eluent of ethyl acetate and petroleum ether. Melting points were determined on a Mel-Temp apparatus and were not corrected. All reactions were monitored by thin layer chromatography (TLC) with silica gel-coated plates and products were visualized using UV light and I_2.

General Procedure for the Synthesis of RC-type Tetra-substituted Alkenes 3 and 3'. The reaction was carried out with **1a** (62.15 mg, 0.30 mmol) and nitroolefin **2** (0.20 mmol) in the presence of PPh_3 (10.49 mg, 0.04 mmol) in CH_2Cl_2 (1.0 ml) at room temperature. The reaction was monitored by TLC until no further increase in the total yield of **3** and **3'** was observed. When the reaction was completed, the resulting mixture was directly subjected to flash chromatography on silica gel (eluted by petroleum ether/ethyl acetate = 14:1) to give the product **3** and **3'**, which were dried under vacuum and further analyzed by ^{1}H NMR, ^{13}C NMR, HRMS analysis.

General Procedure for the Synthesis of 3-Allylic Type Oxindole Derivatives 5. The reaction was carried out with **1a** (62.15 mg, 0.30 mmol) and 3-alkenyl substituted oxindole **4** (0.20 mmol) in the presence of DABCO (4.49 mg, 0.04 mmol) in CH_2Cl_2 (1.0 ml) at 0°C. The reaction was monitored by TLC until no further increase in the yield of **5** was observed. When the reaction was completed, the resulting mixture was directly subjected to flash chromatography on silica gel (eluted by petroleum ether/ethyl acetate = 13:1) to give the major RC-type product **5**, which was dried under vacuum and further analyzed by ^{1}H NMR, ^{13}C NMR, HRMS analysis.

General Procedure for the Synthesis of Chiral RC-type Tetra-substituted Alkene 3. The reaction was carried out with **1a** (31.07 mg, 0.15 mmol) and nitroolefin **2** (0.1 mmol) in the presence of catalyst **C8** (12.61 mg, 0.02 mmol) in dry CH_2Cl_2 (1.0 ml) at room temperature. The reaction was monitored by TLC until no further increase in the yield of **3** was observed. When the reaction was completed, the resulting mixture was directly subjected to flash chromatography on silica gel (eluted by petroleum ether/ethyl acetate = 14:1) to give the product chiral **3**, which was dried under vacuum and further analyzed by ^{1}H NMR, ^{13}C NMR, HRMS and chiral HPLC analysis.

Asymmetric Synthesis of Fully Substituted Cyclohexane-based Spiropyrazolone 8a. The reaction was carried out with chiral **3i** (41.64 mg, 0.10 mmol) and (Z)-4-benzylidene-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one **7a** (31.48 mg, 0.12 mmol) in the presence of triethylamine (2.02 mg, 0.02 mmol) in CH_2Cl_2 (1.0 ml) at room temperature for 8 h. The

reaction was monitored by TLC. When the reaction was completed, the resulting mixture was directly subjected to flash chromatography on silica gel (eluted by petroleum ether/ethyl acetate = 12:1) to give the product **8a**, which was dried under vacuum and further analyzed by ^{1}H NMR, ^{13}C NMR, HRMS and chiral HPLC analysis. Compound **8a** was obtained as a white solid in 44% yield (38.02 mg) for two steps after flash chromatography. The dr value was calculated to be 10:1 from ^{1}H NMR analysis. The enantiomeric excess was determined to be 90% by HPLC (Chiralpak AD-H column, 20% 2-propanol/n-hexane, flow rate 1 ml/min, UV 254 nm): t_{minor} = 7.83 min, t_{major} = 10.36 min. m.p. 171-173 °C; $[\alpha]_D^{20}$: -33.84 (*c* 0.09 in CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44-7.41 (m, 2H), 7.39-7.36 (m, 2H), 7.25-7.23 (m, 2H), 7.22-7.17 (m, 2H), 7.07-6.95 (m, 4H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.98 (t, *J* = 12.0 Hz, 1H), 5.31 (d, *J* = 12.0 Hz, 1H), 4.43-4.37 (m, 1H), 4.34-4.28 (m, 2H), 4.09 (d, *J* = 11.4 Hz, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.51 (d, *J* = 13.8 Hz, 1H), 3.23 (d, *J* = 13.8 Hz, 1H), 2.22 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.57, 167.67, 156.57, 149.86, 149.72, 136.08, 130.72, 130.02, 129.32, 129.05, 127.00, 125.77, 125.26 (d, J_{CF} = 286.5 Hz), 120.65, 115.21, 111.71, 88.75, 62.88, 59.63, 56.12, 55.84, 52.88 (q, J_{CF} = 23.7 Hz), 47.16, 44.92, 34.38, 32.06, 18.32, 13.94 ppm. ESI HRMS: calcd. For $C_{35}H_{33}F_4NO_7Na^+$ 701.2199, found 701.2198.

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Keywords: cross Rauhut-Currier-type reaction; organocatalysis; tri-substituted alkene; asymmetric synthesis; bifunctional H-bonding-tertiary amine

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[29] CCDC 1571411 (**8a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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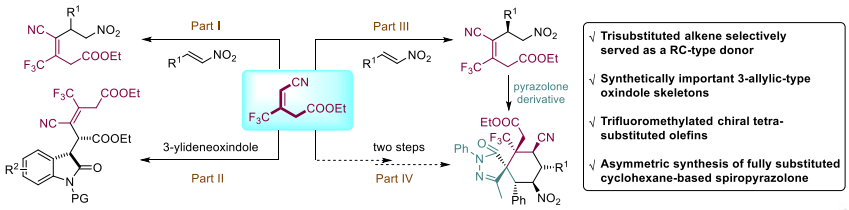

A chemoselective cross RC-type reaction has been developed involving a tri-substituted alkene (CF_3-containing acrylonitrile derivative) is described. This approach can support the synthesis of trifluoromethylated tetra-substituted olefins and 3-allylic-type oxindole skeletons. The transformation of multi-functionalized chiral RC-type product leads to pharmacologically interesting cyclohexane-based spiro-pyrazolones bearing six contiguous chiral centers.

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